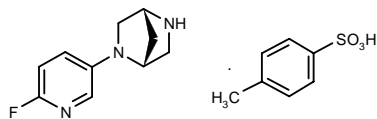


ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

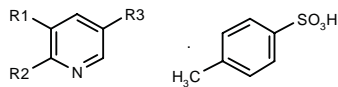
293040

(1*R*,4*R*)-2-(6-Fluoropyridin-3-yl)-2,5-diazabicyclo[2.2.1]-
heptane 4-methylbenzenesulfonate



C10 H12 F N3 . C7 H8 O3 S; Mol wt: 365.4270

ACTION – Nicotinic acetylcholine receptor ligand found to inhibit the binding of [³H]-cytisine to neuronal nicotinic acetylcholine receptors using crude synaptic membrane preparations from whole rat brain (K_i = 0.03 nM). This compound was active as an analgesic agent in the mouse hot-plate assay, with a minimal effective dose (MED) of 0.62 μmol/kg i.p. Other exemplified *N*-substituted diaza-bicyclic compounds include the following:



Compound	R1	R2	R3	Formula
293044	H	Cl	(1 <i>R</i> ,4 <i>R</i>)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl	C ₁₀ H ₁₂ ClN ₃ ·C ₇ H ₈ O ₃ S
293046	CN	H	(1 <i>R</i> ,4 <i>R</i>)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl	C ₁₁ H ₁₂ N ₄ ·C ₇ H ₈ O ₃ S
293047	H	H	3,7-diaza-bicyclo[3.3.1]nonan-2-yl	C ₁₂ H ₁₇ N ₃ ·C ₇ H ₈ O ₃ S

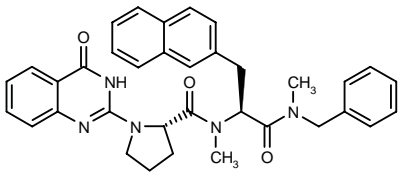
SOURCE – Abbott.

REFERENCES

1. Bunnelle, W.H. et al. (Abbott Laboratories Inc.) *Diazabicyclic derivs. as nicotinic acetylcholine receptor ligands*. WO 0044755.

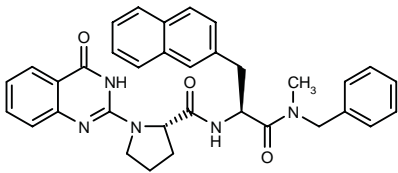
293300

N-(4-Oxo-3,4-dihydroquinazolin-2-yl)-*L*-prolyl-*N*-methyl-*L*-3-(2-naphthyl)alanine *N*-benzyl-*N*-methylamide



C35 H35 N5 O3; Mol wt: 573.6935

ACTION – Orally active tachykinin NK₁ receptor antagonist also reported to possess P-glycoprotein-blocking activity. *In vivo*, compound proved to be about 100-fold more potent than aspirin in reducing mechanical hyperalgesia following oral administration. Another exemplified compound from this series of *N*-heteroaryl substituted proline derivatives is:



293301: C34 H33 N5 O3

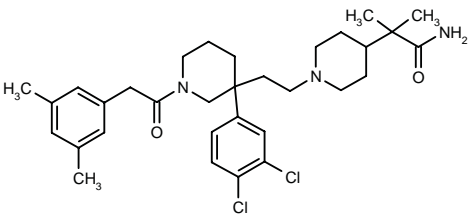
SOURCE – Novartis.

REFERENCES

1. Walpole, C.S.J. et al. (Novartis AG) *Tachykinin antagonists*. US 6107293, WO 9831704.

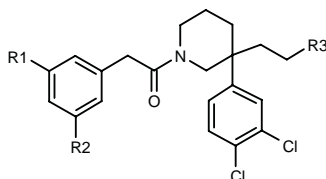
293548

(-)-2-[1-[2-[3-(3,4-Dichlorophenyl)-1-[2-(3,5-dimethylphenyl)acetyl]piperidin-3-yl]ethyl]piperidin-4-yl]-2-methylpropionamide



C32 H43 Cl2 N3 O2; Mol wt: 572.6167

ACTION – Selective NK₁ receptor antagonist reported to exhibit good oral bioavailability, with potential for the treatment of substance P (NK₁ receptor)-mediated disorders such as respiratory, gastrointestinal, urinary, immune, cardiovascular and CNS disorders, pain, migraine, inflammation, nausea, vomiting and skin disorders. Other compounds from this series of (1-phenacyl-3-phenyl-3-piperidylethyl)piperidine derivatives include the following:



Compound	R1=R2	R3	Formula
293550	Cl	4-[NH2COC(Me)2]-1-Pip	C ₃₀ H ₃₇ Cl ₄ N ₃ O ₂
293551	Me	4-[1-(NH2CO)-1-cyclohexyl]-1-Piz	C ₃₄ H ₄₆ Cl ₂ N ₄ O ₂
293552	Cl	4-[N(Me)2COC(Me)2]-1-Piz	C ₃₁ H ₄₀ Cl ₄ N ₄ O ₂
293553	CF ₃	4-[1-(NH2CO)-1-cyclohexyl]-1-Piz	C ₃₄ H ₄₀ Cl ₂ F ₆ N ₄ O ₂
293554	Me	4-[1-(NH2CO)-1-cyclopropyl]-1-Pip	C ₃₂ H ₄₁ Cl ₂ N ₃ O ₂
293555	Et	4-[NH2COC(Me)2]-1-Piz	C ₃₃ H ₄₆ Cl ₂ N ₄ O ₂

SOURCE – Sanofi-Synthélabo.

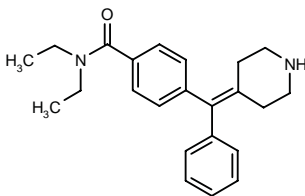
REFERENCES

1. Ducoux, J.P. et al. (Sanofi-Synthélabo) (1-Phenacyl-3-piperidylethyl)piperidine derivs., method for the production thereof and pharmaceutical compns. containing the same. WO 0047572.

ARM-390

293598

N,N-Diethyl-4-[1-phenyl-1-(4-piperidinylidene)methyl]-benzamide



C₂₃ H₂₈ N₂ O; Mol wt: 348.4872

ACTION – Nonpeptide delta opioid receptor (DOP) agonist with low nanomolar binding affinity for human DOP receptors (IC₅₀ = 0.87 nM), high selectivity over human mu (MOP; IC₅₀ = 3800 nM) and kappa opioid receptors (KOP; IC₅₀ = 7470 nM) and full agonist activity (EC₅₀ = 7.2 nM) in functional tests. Compound exhibited excellent oral bioavailability in rats (90-100%) and oral activity in acute and chronic pain models. It induced antinociceptive effects in the mouse abdominal constriction assay (ED₅₀ = 6.0, 17.1 and 14.4 μmol/kg after i.p., s.c. and p.o. administration, respectively) and in two rat models of chronic pain: Freund's complete adjuvant-induced paw inflammation (ED₅₀ = 46.8, 20.4 and 84.2 μmol/kg s.c., i.v. and p.o., respectively) and sciatic nerve cuff-induced neuropathy (ED₅₀ = 17.2, 20.8 and 81.4 μmol/kg s.c., i.v. and p.o., respectively). At analgesic doses compound did not produce respiratory

depression, sedation or motor incoordination. Selected for further preclinical investigation for development as a potential agent for the treatment of chronic and neuropathic pain.

SOURCE – AstraZeneca.

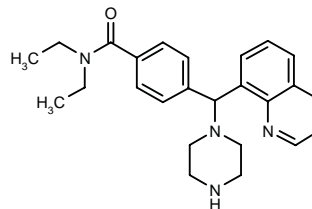
REFERENCES

1. Delorme, D. et al. (AstraZeneca plc; AstraZeneca Canada Inc.) Novel cpds. with analgesic effect. EP 0946511, WO 9828275.
2. Brown, W. et al. A novel class of potent and exceptionally selective, nonpeptidic δ opioid receptor agonist. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-7.
3. Labarre, M. et al. In vitro characterization of ARM390, a new highly selective non-peptide δ opioid receptor agonist. Soc Neurosci Abst 2000, 26(Part 1): Abst 434.17.
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5. Wei, Z.-Y. et al. *N,N*-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A novel, exceptionally selective, potent δ opioid receptor agonist with oral bioavailability and its analogues. J Med Chem 2000, 43(21): 3895.

ARM-434

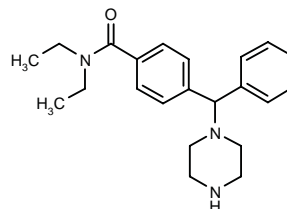
290751

N,N-Diethyl-4-[1-(8-quinolyl)-1-(1-piperazinyl)methyl]-benzamide



C₂₅ H₃₀ N₄ O; Mol wt: 402.5390

ACTION – Nonpeptide delta opioid receptor (DOP) agonist, a derivative of SNC-80 with improved potency and selectivity (IC₅₀ = 0.51, 632 and 7017 nM, respectively, for binding to opioid delta, mu and kappa receptors) and full agonist activity (EC₅₀ = 3.6 nM, E_{max} = 104%) at opioid delta receptors. In addition, compound exhibited greater metabolic stability and improved oral bioavailability (33% in rats) compared to SNC-80. Potentially useful as an analgesic. Another diarylmethyl-piperazine is:



ARM-250 [254335]:* C₂₂ H₂₉ N₃ O

SOURCE – AstraZeneca.

REFERENCES

1. Roberts, E. et al. (AstraZeneca plc) Novel cpds. with analgesic effect. JP 2000502679, US 6130222, WO 9723466.
2. Plobeck, N. et al. New diarylmethylpiperazines as potent and selective nonpeptide δ opioid receptor agonists with increased in vitro metabolic stability. J Med Chem 2000, 43(21): 3878.

3. Plobeck, N. et al. *New diarylmethylpiperazines as selective nonpeptidic δ opioid receptor agonists with improved binding affinity, agonist potency and in vitro metabolic stability*. 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst A-05.

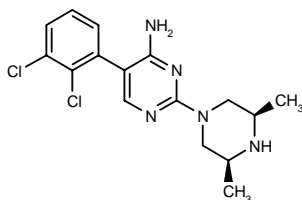
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*Identified compound **254335** (see **254075**) Drug Data Rep 1997, 019(10): 0870.

GW-286103

258534

5-(2,3-Dichlorophenyl)-2-[3(*R*),5(*S*)-dimethylpiperazin-1-yl]pyrimidin-4-amine



C16 H19 Cl2 N5; Mol wt: 352.2671

ACTION – Nonopioid analgesic with the ability to block tetrodotoxin-resistant sodium current in dorsal root ganglion neurons ($K_i = 1 \mu\text{M}$). It fully reversed mechanical hypersensitivity in a chronic constriction injury model of neuropathic pain ($\text{ED}_{50} = 0.48 \text{ mg/kg}$) and was devoid of anticonvulsant activity in the maximal electroshock test at up to 100 mg/kg.

SOURCE – GlaxoSmithKline.

REFERENCES

1. Miller, A.A. et al. (Glaxo Wellcome plc) *Pharmacologically active CNS cpds*. AU 8945964, EP 0372934, EP 0713703, EP 0715851, EP 0727212, EP 0727213, EP 0727214, JP 1990202876, US 5587380, US 5597828, US 5635507, US 5684005.

2. Clare, J.J. et al. *Voltage-gated sodium channels as therapeutic targets*. Drug Discov Today 2000, 5(11): 506.

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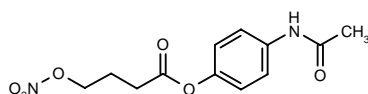
4. *Glaxo Wellcome's R&D pipeline remains full and diverse*. DailyDrugNews.com (Daily Essentials) 1998, Jan 21.

NCX-701

290923

4-(Nitrooxy)butyric acid 4-acetamidophenyl ester

NO-Paracetamol



C12 H16 N2 O6; Mol wt: 284.2664

ACTION – Analgesic and antiinflammatory agent, a nitric oxide (NO)-releasing derivative of paracetamol with superior activity in inhibiting inflammation and reducing pain in experimental models. The compound was found to inhibit carrageenan-induced hind paw edema and mechanical hyperalgesia in rats with ED_{50} values of 169.4 and 156 $\mu\text{mol/kg}$ i.p., respectively, compared to ED_{50} values of > 1986 and 411.6 $\mu\text{mol/kg}$ i.p., respectively, for paracetamol. In mice, it exhibited superior analgesic activity compared to paracetamol, with respective ED_{50} values of 24.8 and 506 $\mu\text{mol/kg}$ p.o. for inhibition of acetic acid-induced abdominal constriction. Currently in phase I testing.

SOURCE – NicOx.

REFERENCES

1. al-Swayeh, O.A. et al. *Nitroparacetamol exhibits anti-inflammatory and antinociceptive activity*. Br J Pharmacol 2000, 130(7): 1453.

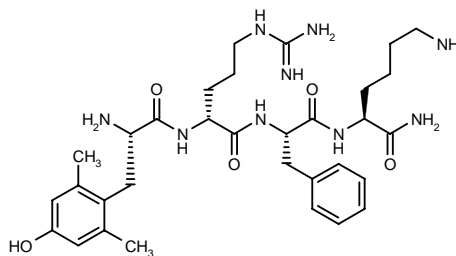
2. *Encouraging preclinical results for NCX-701*. DailyDrugNews.com (Daily Essentials) 2000, June 15.

3. *NicOx advances three products into phase I clinical trials*. DailyDrugNews.com (Daily Essentials) 2000, Dec 19.

SUPER-DALDA¹⁻³

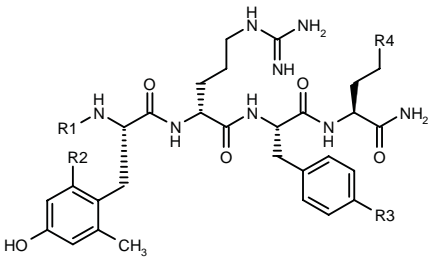
294996

2,6-Dimethyl-L-tyrosyl-D-arginyl-L-phenylalanyl-L-lysineamide



C32 H49 N9 O5; Mol wt: 639.7971

ACTION – Opioid analgesic with high affinity and selectivity for mu opioid receptors (MOP ; $K_i = 0.143 \text{ nM}$). Compound induced a long-lasting analgesic effect in the rat tail-flick test, with extraordinary potency ($\text{ED}_{50} = 1.06 \text{ pmol}$ after intrathecal administration), being 3,000 times more potent than morphine. Unlike morphine, compound did not induce respiratory depression in rats at doses 30-fold higher than its analgesic ED_{50} . In pregnant sheep, compound did not cross the placental barrier and had no effect on maternal and fetal blood pressure, heart rate, blood gases or plasma glucose. Potentially useful for spinal and obstetrical analgesia. Other related analogues of a dermorphin-related tetrapeptide are:



Compound	R1	R2	R3	R4	Formula
294997 ¹⁻³	H	Me	H	CH2NH2	C ₃₁ H ₄₇ N ₉ O ₅
294998 ¹⁻³	H	Me	H	NH2	C ₃₀ H ₄₆ N ₉ O ₅
294999 ¹⁻³	H	H	H	CH2CH2NH2	C ₃₁ H ₄₇ N ₉ O ₅
295001 ¹	H	Me	F	CH2CH2NH2	C ₃₂ H ₄₈ FN ₉ O ₅
295002 ¹⁻³	Me	Me	H	CH2CH2NH2	C ₃₃ H ₅₁ N ₉ O ₅

SOURCE – AstraZeneca.

REFERENCES

1. Schiller, P. (AstraZeneca AB) *DALDA analogs and their use*. WO 0055189.

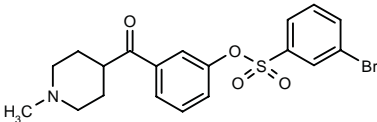
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3. Schiller, P.W. et al. *Synthesis and in vitro opioid activity profiles of DALDA analogues*. Eur J Med Chem 2000, 35(10): 895.

ANTIMIGRAINE DRUGS

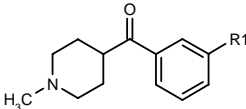
293635

3-Bromobenzenesulfonic acid 3-(1-methylpiperidin-4-yl-carbonyl)phenyl ester



C19 H20 Br N O4 S; Mol wt: 438.3400

ACTION – 5-HT_{1F} receptor agonist with the ability to inhibit peptide extravasation due to stimulation of the trigeminal ganglia, and thus useful for the treatment or prophylaxis of migraine and related disorders. Other exemplified compounds include the following:



Compound	R1	Formula
293636	4-I-Ph-SO ₂ O	C ₁₉ H ₂₀ INO ₄ S
293638	3-NO ₂ -PhNHCSNH	C ₂₀ H ₂₂ N ₄ O ₃ S
293639	2-furyl-NHCSNH	C ₁₈ H ₂₁ N ₃ O ₂ S
293640	4-Pyr-NHCSNH	C ₁₉ H ₂₂ N ₄ OS
293641	3-NO ₂ -PhSO ₂ NH	C ₁₉ H ₂₁ N ₃ O ₅ S
293642	3-Pyr-NHCONH	C ₁₉ H ₂₂ N ₄ O ₂
293644	2-OH-PhSO ₂ NH	C ₁₉ H ₂₂ N ₂ O ₄ S
293645	4-F-PhSO ₂ NH	C ₁₉ H ₂₁ FN ₂ O ₃ S

SOURCE – Lilly.

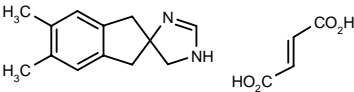
REFERENCES

1. Krushinski, J.H. Jr. et al. (Eli Lilly and Company) *5-HT_{1F} agonists*. WO 0047559.

S-19014

293729

5',6'-Dimethylspiro[4,5-dihydro-1 H-imidazol-4,2'-indane] fumarate



C13 H16 N2 . C4 H4 O4; Mol wt: 316.3550

ACTION – α_1 - And α_2 -adrenoceptor partial agonist able to contract dog saphenous vein (EC₅₀ = 0.04 μ M) without contracting coronary, carotid and femoral arteries. Moreover, compound inhibited human platelet aggregation induced by adrenaline (IC₅₀ = 0.23 μ M). *In vivo* in dogs, it dose-dependently reduced carotid blood flow and subcutaneous temperature and increased arteriovenous oxygen concentration differences, suggesting a selective effect on arteriovenous shunts. Potentially useful for the treatment of migraine.

SOURCE – Servier.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Benzospiroalkene derivs., process for their preparation and pharmaceutical compsns. containing them*. CA 2128359, EP 0635497, FR 2709306, JP 1995304753, US 5436261.

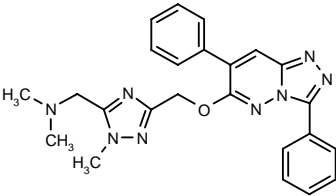
2. Lacoste, J.-M. et al. *Spiro[(1,3-diazacyclopent-1-ene)-5,2'-(5',6'-dimethylindane)]*: A new α -adrenergic partial agonist. Two synthetic approaches. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-83.

PSYCHOPHARMACOLOGIC DRUGS

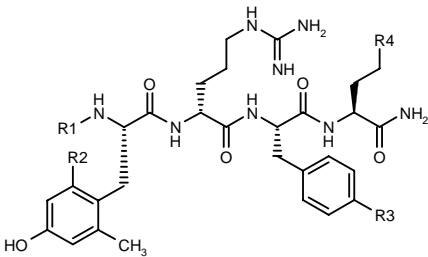
ANXIOLYTICS

293575

N-[3-(3,7-Diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxy-methyl)-1-methyl-1 H-1,2,4-triazol-5-ylmethyl]-N,N-dimethylamine



C24 H24 N8 O; Mol wt: 440.5086



Compound	R1	R2	R3	R4	Formula
294997 ¹⁻³	H	Me	H	CH2NH2	C ₃₁ H ₄₇ N ₉ O ₅
294998 ¹⁻³	H	Me	H	NH2	C ₃₀ H ₄₆ N ₉ O ₅
294999 ¹⁻³	H	H	H	CH2CH2NH2	C ₃₁ H ₄₇ N ₉ O ₅
295001 ¹	H	Me	F	CH2CH2NH2	C ₃₂ H ₄₈ FN ₉ O ₅
295002 ¹⁻³	Me	Me	H	CH2CH2NH2	C ₃₃ H ₅₁ N ₉ O ₅

SOURCE – AstraZeneca.

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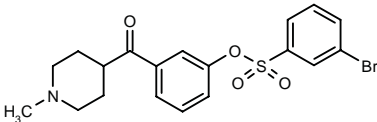
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ANTIMIGRAINE DRUGS

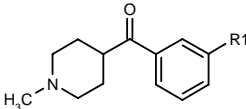
293635

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293640	4-Pyr-NHCSNH	C ₁₉ H ₂₂ N ₄ OS
293641	3-NO ₂ -PhSO ₂ NH	C ₁₉ H ₂₁ N ₃ O ₅ S
293642	3-Pyr-NHCONH	C ₁₉ H ₂₂ N ₄ O ₂
293644	2-OH-PhSO ₂ NH	C ₁₉ H ₂₂ N ₂ O ₄ S
293645	4-F-PhSO ₂ NH	C ₁₉ H ₂₁ FN ₂ O ₃ S

SOURCE – Lilly.

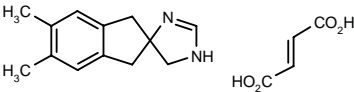
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S-19014

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ACTION – α_1 - And α_2 -adrenoceptor partial agonist able to contract dog saphenous vein (EC₅₀ = 0.04 μ M) without contracting coronary, carotid and femoral arteries. Moreover, compound inhibited human platelet aggregation induced by adrenaline (IC₅₀ = 0.23 μ M). *In vivo* in dogs, it dose-dependently reduced carotid blood flow and subcutaneous temperature and increased arteriovenous oxygen concentration differences, suggesting a selective effect on arteriovenous shunts. Potentially useful for the treatment of migraine.

SOURCE – Servier.

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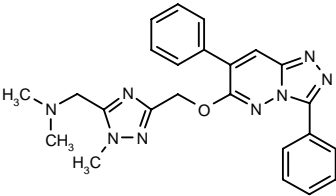
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PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

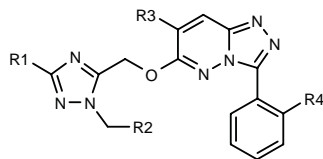
293575

N-[3-(3,7-Diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxy-methyl)-1-methyl-1 H-1,2,4-triazol-5-ylmethyl]-N,N-dimethylamine



C24 H24 N8 O; Mol wt: 440.5086

ACTION – Selective ligand for GABA_A receptors with particularly good binding affinity for the α2 and/or α3 subunit. This compound may be of use for the treatment of a variety of CNS disorders, preferably for the treatment or prevention of anxiety. Other specifically claimed triazolo-pyridazine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
293576	CH2OH	H	1-pyrrolidinyl	H	C ₂₀ H ₂₂ N ₈ O ₂
293577	4-morpholinyl-CH2	H	1-pyrrolidinyl	H	C ₂₄ H ₂₉ N ₉ O ₂
293578	3,3-(F)2-1-azetidiny-CH2	H	1-pyrrolidinyl	H	C ₂₃ H ₂₆ F ₂ N ₉ O
293579	CH2OH	H	t-Bu	F	C ₂₀ H ₂₂ FN ₇ O ₂
293580	CF3	H	t-Bu	F	C ₂₀ H ₁₉ F ₄ N ₇ O
293581	CF3	Me	t-Bu	F	C ₂₁ H ₂₁ F ₄ N ₇ O

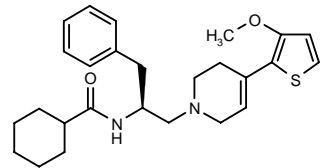
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 0047582.

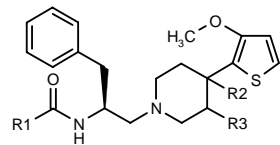
293622

N-[1(*S*)-Benzyl-2-[4-(3-methoxythien-2-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]cyclohexanecarboxamide



C26 H34 N2 O2 S; Mol wt: 438.6326

ACTION – Serotonergic agent with high affinity for 5-HT_{1A} receptors, as demonstrated *in vitro* by its ability to displace [³H]-8-OH-DPAT from this receptor (IC₅₀ = 0.78 nM). As such, the compound is potentially useful for the treatment of CNS disorders, especially psychosis, depression and anxiety. Other specifically claimed compounds within this series of *N*-substituted-4-(thien-2-yl)-piperidines and tetrahydropyridines are:



Compound	R1	R2	R3	Formula
293623	t-BuO	OH	H	C ₂₄ H ₃₄ N ₂ O ₄ S
293624	t-BuO	bond		C ₂₄ H ₃₂ N ₂ O ₃ S
293625	cyclohexyl	H	H	C ₂₆ H ₃₆ N ₂ O ₂ S

SOURCE – American Home Products.

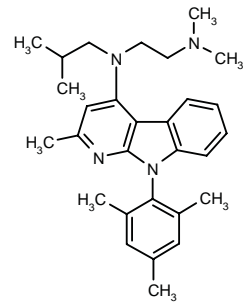
REFERENCES

1. Baudy, R.B. et al. (American Home Products Corp.) *N-Substd. (thiophen-2-yl)-piperidines and tetrahydropyridines as serotonergic agents*. US 6110943.

NGD-98-1*

281950

N-[2-(Dimethylamino)ethyl]-*N*-isobutyl-*N*-[2-methyl-9-(2,4,6-trimethylphenyl)-9*H*-pyrido[2,3-*b*]indol-4-yl]amine



C29 H38 N4; Mol wt: 442.6472

ACTION – Potent and selective corticotropin-releasing factor CRF₁ receptor antagonist (K_i = 4.2 nM) able to antagonize CRF-induced behavioral effects in rats including enhancement of acoustic startle and of shock-elicited startle and induction of grooming (MED = 20, 40 and 20 mg/kg p.o., respectively). In addition, compound was active in a number of behavioral tests predictive of antidepressant or anxiolytic activity such as separation-induced vocalization in rat pups, the Vogel lick suppression test, yohimbine-enhanced startle and shock-elicited startle (MED = 20, 10, 5 and 5 mg/kg i.p., respectively). At higher doses (> 40 mg/kg), it did not show signs of sedation, muscle relaxation or cognitive impairment. Potentially useful for the treatment of neuropsychiatric disorders such as anxiety and depression.

SOURCE – Neurogen.

REFERENCES

1. Horvath, R.F. et al. (Neurogen Corp.) *Aminoalkyl substd. 9H-pyridino[2,3-b]indole and 9H-pyrimidino[4,5-b]indole derivs*. EP 1068207, US 6147085, WO 9951600.

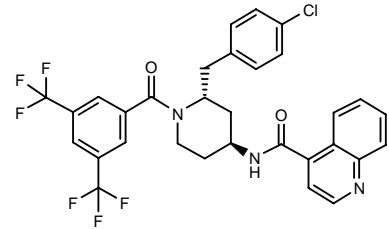
2. Horvath, R.F. and Hutchison, A.J. *Tricyclic CRF receptor ligands*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-82.

*Identified compound **281950** (see **281947**) Drug Data Rep 2000, 022(02): 0124.

NKP-608*

236430

(2*R*,4*S*)-*N*-[1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chlorobenzyl)piperidin-4-yl]quinoline-4-carboxamide



C31 H24 Cl F6 N3 O2; Mol wt: 619.9990

ACTION – Potent, nonpeptide tachykinin NK₁ receptor antagonist with strong antidepressant-like activity in a validated rat model of chronic mild stress in which a range of conventional antidepressants have been shown to be effective. Daily oral administration of compound for 5 weeks was found to reverse the reduction in sucrose consumption in these animals: a dose of 0.03 mg/kg/day produced a complete reversal after 4 weeks of treatment and the higher dose of 0.1 mg/kg/day showed a similar effect after only 1 week of treatment. Compound showed a more rapid onset of action than imipramine (10 mg/kg), which required 5 weeks for full reversal. Compound is in phase II clinical studies for the treatment of social phobia.

SOURCE – Novartis.

REFERENCES

1. Färber, L. (Novartis AG) *Pharmaceutical uses*. WO 0010545.

2. Lang, S. and Liechti, K. (Novartis AG) *Microemulsion preconcentrates containing a piperidine substance P antagonist*. FR 2779145, WO 9961025.

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5. Lewis, C.A. et al. *Pharmacology of NKP608, a novel selective neurokinin-1 receptor antagonist with oral activity*. Br J Pharmacol 2000, 131(Suppl.): Abstr 118P.

6. Papp, M. et al. *The NK1-receptor antagonist NKP608 has an antidepressant-like effect in the chronic mild stress model of depression in rats*. Behav Brain Res 2000, 115(1): 19.

7. Reinhardt, J. *Innovation and productivity drive sustained growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.

8. Vassout, A. et al. *NKP608: A selective NK-1 receptor antagonist with anxiolytic-like effects in the social interaction and social test in rats*. Regul Pept 2000, 96(1-2): 7.

9. *Novartis: Operational Review 1998*. DailyDrugNews.com (Daily Essentials) 1999, May 7.

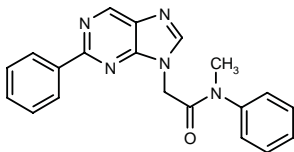
10. *Novartis R&D day 1999: Innovation drives future growth*. DailyDrugNews.com (Daily Essentials) 1999, Sept 24.

*Identified compound **236430** Drug Data Rep 1996, 018(07): 0588.

SX-4699

293596

N-Methyl-*N*-phenyl-2-(2-phenyl-9*H*-purin-9-yl)acetamide



C20 H17 N5 O; Mol wt: 343.3883

ACTION – Potential anxiolytic agent, a 2-phenylpurine derivative with high affinity for the mitochondrial benzodiazepine receptor (IC₅₀ = 0.88 nM vs. 41 nM for diazepam) and over 1,000-fold selectivity over central benzodiazepine sites. Compound exhibited high oral efficacy in a series of animal models predictive of anxiolytic-like effects including the light-dark box test in mice, the Vogel conflict test in rats and the social interaction test in mice (ED₅₀ = 0.1 mg/kg p.o. in all tests; ED₅₀ = 1, 5 and 0.03 mg/kg p.o., respectively, for diazepam). No muscle relaxation or memory deficits were seen in rats and mice at up to 1000 mg/kg p.o.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

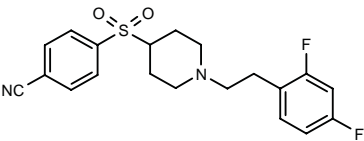
1. Murata, T. et al. (Dainippon Pharmaceutical Co., Ltd.) *2-Arylpurine-9-acetamide derivs., process for the preparation thereof, medicinal compns. containing the same and intermediates of the derivs.* WO 0073306.

2. Kondoh, K. et al. *Novel 2-phenylpurine derivatives as mitochondrial benzodiazepine receptor ligands*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abstr PB-87.

ANTIPSYCHOTIC DRUGS

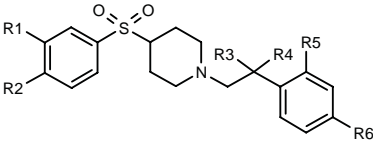
292823

4-[1-[2-(2,4-Difluorophenyl)ethyl]piperidin-4-ylsulfonyl]-benzonitrile



C20 H20 F2 N2 O2 S; Mol wt: 390.4520

ACTION – Selective 5-HT_{2A} receptor antagonist for the treatment of CNS disorders, especially schizophrenia. Other specifically claimed phenylsulfonyl derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
292824	H	1-imidazolyl	H	H	F	F	C ₂₂ H ₂₃ F ₂ N ₃ O ₂ S
292825	H	2-Me-5-tetrazolyl	H	H	F	F	C ₂₁ H ₂₃ F ₂ N ₅ O ₂ S
292827	H	CONH2	H	H	Cl	H	C ₂₀ H ₂₃ ClN ₂ O ₃ S
292828	CONH2	H	H	H	F	F	C ₂₀ H ₂₂ F ₂ N ₂ O ₃ S
292829	H	H	-O-	H	Cl	Cl	C ₁₉ H ₂₀ ClNO ₃ S

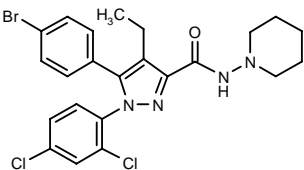
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Blurton, P. et al. (Merck Sharp & Dohme Ltd.) *Phenylsulphonyl derivs. as 5-HT receptor ligands*. WO 0043362.

293160

5-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-(1-piperidinyl)-1*H*-pyrazole-3-carboxamide



C23 H23 Br Cl2 N4 O; Mol wt: 522.2717

ACTION – Selective cannabinoid CB₁ receptor antagonist with superior potency and a longer duration of action than the reference compound SR-141716, expected to be useful for the treatment of psychotic disorders, eating disorders, obesity, cognitive disorders, alcoholism and nicotine addiction. *In vitro*, compound exhibited a K_i value of 5.4 nM for human CB₁ receptors, compared to a K_i value of 34 nM for SR-141716. When tested in a binding assay *in vivo* in mice at 10 mg/kg p.o., compound gave 82 and 44% CB₁ receptor occupancy, respectively, at 1 and 24 h postadministration, compared to 69 and 4% occupancy, respectively, for SR-141716 at the same dose. When tested in a hypothermia model in mice induced by Win-55212-2, compound exhibited an ED₅₀ value of 0.3 mg/kg p.o. versus 0.4 mg/kg p.o. for SR-141716, with a significantly increased duration of action, being active at 24 h postadministration when given at 1 mg/kg p.o., whereas reference compound at this dose was inactive.

SOURCE – Sanofi-Synthélabo.

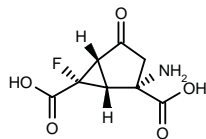
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MGS-0028*,1,3-6

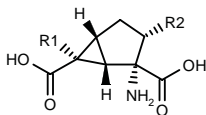
286777

(1*R*,2*S*,5*S*,6*S*)-2-Amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid



C8 H8 F N O5; Mol wt: 217.1512

ACTION – Potent and selective group II metabotropic glutamate receptor (mglu₂, mglu₃) agonist with K_i values of 3.3 and 3.62 nM, respectively, for mglu₂ and mglu₃ receptors in binding assays and respective EC₅₀ values of 0.57 and 2.07 nM for functional agonist activity in CHO cells expressing mglu₂ and mglu₃ receptors; in contrast, EC₅₀ values at other mglu receptors (mglu₄, mglu₆, mglu₇, mglu₅ and mglu_{1a}) were > 10,000 nM). Compound exhibited strong oral activity in antagonizing phencyclidine-induced hyperactivity and head-weaving behavior in rats, giving ED₅₀ values of 0.30 mg/kg and 0.090 µg/kg, respectively. Potentially useful for the treatment of schizophrenia. Other related compounds include the following:



Compound	R1	R2	Formula
MGS-0008 [280539]**,2-5	H	F	C ₈ H ₁₀ FNO ₄
MGS-0022 [286779]****,1,4-6	F	H	C ₈ H ₁₀ FNO ₄

SOURCE – Taisho.

REFERENCES

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2. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.) *Fluorine-containing amino acid derivs.* EP 1052246, JP 1999279129, WO 9938839.

3. Kumagai, T. et al. *Synthesis, SAR and pharmacological characterization of 2-amino-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent, selective and orally active group II metabotropic glutamate receptor agonists.* 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 1P-23.

4. Nakazato, A. et al. *Synthesis, SAR and biological activities of potent and selective group II metabotropic glutamate receptor antagonists, novel 2-amino-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-104.

5. Nakazato, A. et al. *Synthesis, SAR, and biological activities of potent and selective group II mGluR agonists, novel 2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 104.

6. Nakazato, A. et al. *Synthesis, SARs, and pharmacological characterization of 2-amino-3 or 6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent, selective, and orally active group II metabotropic glutamate receptor agonists.* J Med Chem 2000, 43(25): 4893.

*Identified compound **286777** Drug Data Rep 2000, 022(06): 0502.

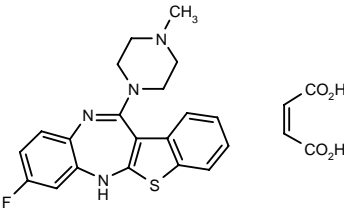
Identified compound **280539 Drug Data Rep 1999, 021(11): 0960.

***Identified compound **286779** (see **286777**) Drug Data Rep 2000, 022(06): 0502.

Y-931

293826

8-Fluoro-12-(4-methylpiperazin-1-yl)-6*H*-[1]benzothieno[2,3-*b*][1,5]benzodiazepine maleate



C20 H19 F N4 S . C4 H4 O4; Mol wt: 482.5337

ACTION – Antipsychotic agent that interacts with several neurotransmitter receptors and exerts a potent antagonist effect at dopamine D2 receptors (K_i = 3.5 nM; ED₅₀ = 2.4 mg/kg p.o. against apomorphine-induced hyperactivity in rats), without inducing catalepsy. Moreover, compound was able to inhibit NMDA receptor hypofunction induced by the selective, noncompetitive NMDA receptor antagonist MK-801, as demonstrated by inhibition of MK-801-induced neuronal vacuolization in rat brain, being more potent than clozapine or other antipsychotics (ED₅₀ = 0.20, 5.7, 1.1 and 19 mg/kg p.o., respectively, for Y-931, clozapine, olanzapine and haloperidol).

SOURCE – Welfide.

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1. Seio, K. et al. (Welfide Corporation) *Fused thiophene cpds. and medicinal use thereof.* EP 1016664, WO 9911647.

2. Ai, J. et al. *Biphasic modulation of NMDA-induces responses in pyramidal cells of the medial prefrontal cortex by Y-931, a potential atypical antipsychotic drug.* Soc Neurosci Abst 2000, 26(Part 1): Abst 97.14.

3. Morimoto, T. et al. *Y-931, a novel antipsychotic with potential property to ameliorate NMDA receptor-hypofunction: I- Receptorial and pharmacological profile in comparison with clozapine and haloperidol.* Soc Neurosci Abst 2000, 26(Part 1): Abst 97.15.

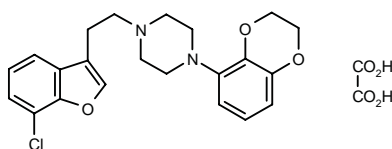
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5. Tanaka, H. et al. Y-931, a novel antipsychotic with potential anti-NRH (NMDA receptor-hypofunction) activity: Synthesis and structure-activity relationships of 6H-[1]benzothieno[2,3-b][1,5]benzodiazepines. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-128.

TREATMENT OF MOOD DISORDERS

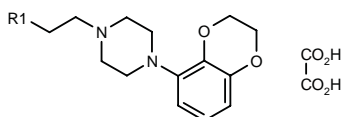
292797

1-[2-(7-Chlorobenzofuran-3-yl)ethyl]-4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine oxalate



C22 H23 Cl N2 O3 . C2 H2 O4; Mol wt: 488.9215

ACTION – Dual-action compound that acts as a 5-HT_{1A} receptor antagonist and a 5-HT reuptake inhibitor. The compound demonstrated affinity for 5-HT_{1A} receptors by inhibiting the binding of [³H]-5-carboxamidotryptamine to cloned human receptors expressed in transfected HeLa cells (IC₅₀ = 2.1 nM); its 5-HT_{1A} receptor-antagonist activity was determined by its ability to antagonize the 5-HT-induced inhibition of forskolin-stimulated cAMP accumulation, giving an IC₅₀ value of 1.5 μM. Its ability to inhibit 5-HT accumulation was determined *in vitro* in rat brain synaptosomes (IC₅₀ = 1.5 nM). Particularly useful for the treatment of depression, especially when a fast onset of antidepressive effect is required or in patients who are resistant to treatment with other antidepressants. Other exemplified compounds are:



Compound	R1	Formula
292798	1-indenyl-CH2CH2	C ₂₅ H ₃₀ N ₂ O ₂ ·C ₂ H ₂ O ₄
292799	5-F-3-benzofuryl	C ₂₂ H ₂₃ FN ₂ O ₃ ·C ₂ H ₂ O ₄
292800	4-Me-3-benzofuryl-CH2	C ₂₄ H ₂₈ N ₂ O ₃ ·C ₂ H ₂ O ₄

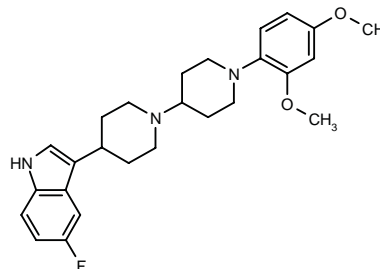
SOURCE – Lundbeck.

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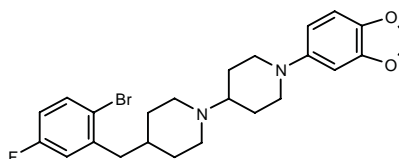
293028

3-[1-[1-(2,4-Dimethoxyphenyl)piperidin-4-yl]piperidin-4-yl]-5-fluoro-1H-indole



C26 H32 F N3 O2; Mol wt: 437.5558

ACTION – Potent 5-HT reuptake inhibitor (K_i < 100 nM), potentially useful for the treatment of depression. Another specifically claimed heterocyclic compound is:



293030: C24 H28 Br F N2 O2

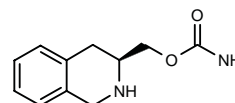
SOURCE – Bristol-Myers Squibb.

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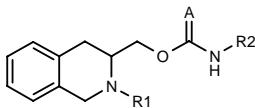
293168

Carbamic acid 1,2,3,4-tetrahydroisoquinolin-3(S)-ylmethyl ester



C11 H14 N2 O2; Mol wt: 206.2436

ACTION – An inhibitor of monoamine oxidase type A (MAO-A; 97.7% inhibition in rat liver mitochondrial membranes at 10 μM), reported to exhibit low toxicity. When tested *in vivo* in mice, compound produced a 238% increase in 5-HTP-induced head twitch responses at 1 mg/kg p.o. and reduced immobility time by 83% in the forced swimming test at 60 mg/kg p.o. Potentially useful for the treatment of CNS disorders such as depression, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, panic attacks, anxiety, epilepsy, stroke, obesity and pain. Other compounds from this series of tetrahydroisoquinolinealkanol derivatives include the following:



Compound	R1	R2	A	Isomer	Formula
293169	H	H	O	R	C ₁₁ H ₁₄ N ₂ O ₂
293170	H	H	O		C ₁₁ H ₁₄ N ₂ O ₂
293171	Me	H	O	S	C ₁₂ H ₁₆ N ₂ O ₂
293172	H	H	S		C ₁₁ H ₁₄ N ₂ OS
293173	H	Me	S	S	C ₁₂ H ₁₆ N ₂ OS
293174	CONHPh	Me	S	S	C ₁₉ H ₂₁ N ₃ O ₂ S
293175	Me	Me	S	S	C ₁₃ H ₁₈ N ₂ OS

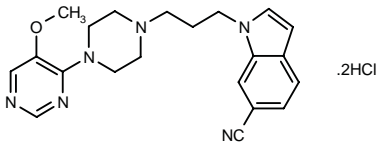
SOURCE – SK Corp.

REFERENCES

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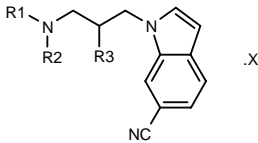
293244

1-[3-[4-(5-Methoxypyrimidin-4-yl)piperazin-1-yl]propyl]-1*H*-indole-6-carbonitrile dihydrochloride



C21 H24 N6 O . 2HCl; Mol wt: 449.3834

ACTION – Dual 5-HT reuptake inhibitor and 5-HT_{2C} receptor ligand with potential for the treatment of depression, panic attacks, obsessive–compulsive disorders, phobia, drug addiction, bulimia and anxiety. Compound exhibited a K_i value of 9.8 nM for 5-HT reuptake sites in rat cortical membranes and is reported to bind to 5-HT_{2C} receptors with K_i values in the range 1-10 nM. Other specifically claimed compounds from this series of cyanoindole derivatives are:



Compound	R1	R2	R3	X	Formula
293245	Me	Me	H	HCl	C ₁₄ H ₁₇ N ₃ .HCl
293246	CH2CH2Cl	-(CH2)2-			C ₁₆ H ₁₈ ClN ₃

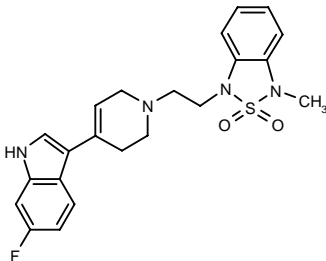
SOURCE – ADIR.

REFERENCES

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293816

1-[2-[4-(6-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-3-methyl-1,3-dihydro-2,1,3-benzothiadiazole-2,2-dioxide



C22 H23 F N4 O2 S; Mol wt: 426.5137

ACTION – Serotonergic modulator that exhibits high affinity for 5-HT_{2A} receptors (K_i < 15 nM against [³H]-ketanserin binding to human 5-HT_{2A} receptors) and which also inhibits 5-HT reuptake. Potentially useful for the treatment of a wide range of conditions such as depression, obesity, bulimia, alcoholism, pain, hypertension, aging, memory loss, sexual dysfunction, anxiety, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, Alzheimer’s disease and sleep disorders.

SOURCE – Lilly.

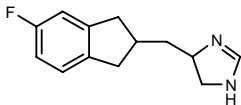
REFERENCES

1. Fairhurst, J. (Eli Lilly and Company) *1-((Indolyl azacycloalkyl)alkyl)-2,1,3-benzothiadiazole 2,2-dioxides exhibiting 5-HT_{2A} receptor activity.* WO 0049017.

S-34324

293595

4-(5-Fluoroindan-2-ylmethyl)-4,5-dihydro-1*H*-imidazole



C13 H15 F N2; Mol wt: 218.2735

ACTION – Potential antidepressant, an inhibitor of presynaptic α₂-adrenoceptors (pK_i = 8.1) with inhibitory activity against 5-HT and noradrenaline uptake (pK_i = 7.6 and 6.5, respectively). At a dose of 10 mg/kg i.p., it was associated with increases of 260, 800 and 2400%, respectively, in mouse brain levels of 5-HT, dopamine and noradrenaline. In a mouse model of aggression, a behavioral model predictive of antidepressant activity, compound at a dose of 1.1 mg/kg i.p. was found to reduce the duration and the number of attacks by 50%.

SOURCE – Servier.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Imidazoline derivs., preparation and pharmaceutical compsns. containing them.* EP 1010693, FR 2787451, JP 2000178255, US 6127396.

2. Cordi, A. et al. *Search for novel antidepressants through synergy between α_2 adrenoceptor antagonism and monoamine uptake inhibition*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-57.

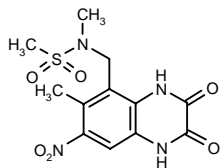
3. Cordi, A.A. et al. *Potential antidepressants displayed combined α_2 -adrenoceptor antagonist and monoamine uptake inhibitor properties*. J Med Chem 2001, 44(5): 787.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

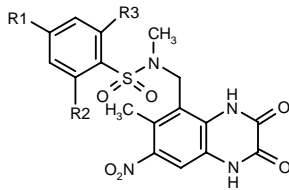
292843

N-Methyl-N-(6-methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)methanesulfonamide



C12 H14 N4 O6 S; Mol wt: 342.3306

ACTION – Neuroprotective agent, a glutamate receptor antagonist with potent binding affinity for AMPA, kainate and glycine-site NMDA receptors (IC₅₀ = 0.21, 0.29 and 0.1 μ M, respectively). The compound demonstrated efficacy in the maximal electroshock seizure (MES) assay in mice and is particularly useful for treating convulsions. Other specifically claimed sulfonamide derivatives of substituted quinoxaline-2,3-diones are:



Compound	R1	R2	R3	Formula
292844	Me	H	H	C ₁₈ H ₁₈ N ₄ O ₆ S
292845	i-Pr	i-Pr	i-Pr	C ₂₆ H ₃₄ N ₄ O ₆ S

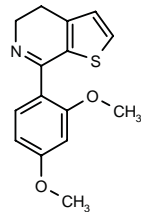
SOURCE – Pfizer.

REFERENCES

1. Kornberg, B.E. and Nikam, S.S. (Pfizer Inc.) *Sulfonamide derivs. of subst. quinoxaline 2,3-diones as glutamate receptor antagonists*. US 6096744.

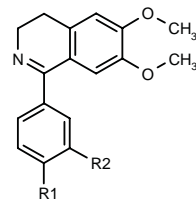
293020

7-(2,4-Dimethoxyphenyl)-4,5-dihydrothieno[2,3-*c*]pyridine

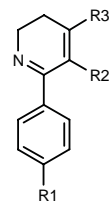


C15 H15 N O2 S; Mol wt: 273.3545

ACTION – Anticonvulsant exhibiting an ED₅₀ of 6.17 mg/kg s.c. in the maximal electroshock seizure (MES) assay in mice. Other specifically claimed fused dihydropyridines include the following:



Compound	R1	R2	Formula
293022	H	OPh	C ₂₃ H ₂₁ NO ₃
293023	H	COPh	C ₂₄ H ₂₁ NO ₃
293024	Et	H	C ₁₉ H ₂₁ NO ₂



Compound	R1	R2	R3	Formula
293025	OBu	-S-CH=CH-		C ₁₇ H ₁₉ NOS
293026	NHCOPh	-S-CH=CH-		C ₂₀ H ₁₈ N ₂ OS
293027	OC5H11	-CH=CH-S-		C ₁₈ H ₂₁ NOS

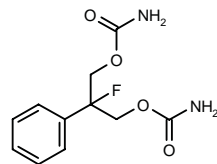
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Arndts, D. et al. (Boehringer Ingelheim Pharma KG) *Fused dihydropyridines and use of fused dihydropyridines in the preparation of agents for the treatment of epilepsy*. DE 19943321, WO 0044725.

293663

2-Fluoro-2-phenylpropane-1,3-diol dicarbamate



C11 H13 F N2 O4; Mol wt: 256.2317

2. Cordi, A. et al. *Search for novel antidepressants through synergy between α_2 adrenoceptor antagonism and monoamine uptake inhibition*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-57.

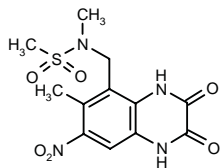
3. Cordi, A.A. et al. *Potential antidepressants displayed combined α_2 -adrenoceptor antagonist and monoamine uptake inhibitor properties*. J Med Chem 2001, 44(5): 787.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

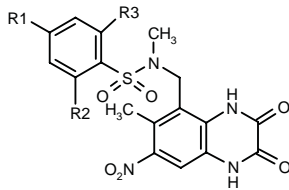
292843

N-Methyl-N-(6-methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)methanesulfonamide



C12 H14 N4 O6 S; Mol wt: 342.3306

ACTION – Neuroprotective agent, a glutamate receptor antagonist with potent binding affinity for AMPA, kainate and glycine-site NMDA receptors (IC₅₀ = 0.21, 0.29 and 0.1 μ M, respectively). The compound demonstrated efficacy in the maximal electroshock seizure (MES) assay in mice and is particularly useful for treating convulsions. Other specifically claimed sulfonamide derivatives of substituted quinoxaline-2,3-diones are:



Compound	R1	R2	R3	Formula
292844	Me	H	H	C ₁₈ H ₁₈ N ₄ O ₆ S
292845	i-Pr	i-Pr	i-Pr	C ₂₆ H ₃₄ N ₄ O ₆ S

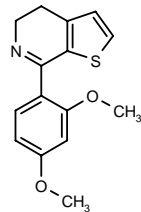
SOURCE – Pfizer.

REFERENCES

1. Kornberg, B.E. and Nikam, S.S. (Pfizer Inc.) *Sulfonamide derivs. of subst. quinoxaline 2,3-diones as glutamate receptor antagonists*. US 6096744.

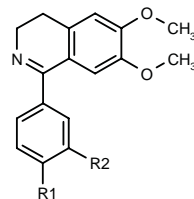
293020

7-(2,4-Dimethoxyphenyl)-4,5-dihydrothieno[2,3-*c*]pyridine

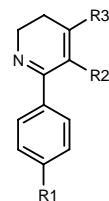


C15 H15 N O2 S; Mol wt: 273.3545

ACTION – Anticonvulsant exhibiting an ED₅₀ of 6.17 mg/kg s.c. in the maximal electroshock seizure (MES) assay in mice. Other specifically claimed fused dihydropyridines include the following:



Compound	R1	R2	Formula
293022	H	OPh	C ₂₃ H ₂₁ NO ₃
293023	H	COPh	C ₂₄ H ₂₁ NO ₃
293024	Et	H	C ₁₉ H ₂₁ NO ₂



Compound	R1	R2	R3	Formula
293025	OBu	-S-CH=CH-		C ₁₇ H ₁₉ NOS
293026	NHCOPh	-S-CH=CH-		C ₂₀ H ₁₈ N ₂ OS
293027	OC5H11	-CH=CH-S-		C ₁₈ H ₂₁ NOS

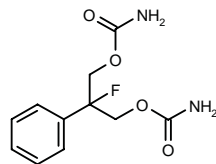
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Arndts, D. et al. (Boehringer Ingelheim Pharma KG) *Fused dihydropyridines and use of fused dihydropyridines in the preparation of agents for the treatment of epilepsy*. DE 19943321, WO 0044725.

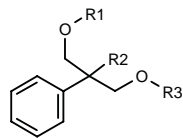
293663

2-Fluoro-2-phenylpropane-1,3-diol dicarbamate

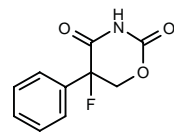


C11 H13 F N2 O4; Mol wt: 256.2317

ACTION – Agent for the treatment of neurological diseases such as epilepsy, as well as for the treatment of tissue damage resulting from ischemic events, a representative compound from a series of felbamate derivatives designed to prevent the formation of metabolites that are believed to be responsible for the toxicity associated with felbamate therapy. *In vivo*, compound exhibited potent anticonvulsant activity in the maximal electroshock seizure (MES) test in mice and rats, giving ED₅₀ values of 27 and 3 mg/kg p.o., respectively, while showing no toxicity at doses up to 218 and 500 mg/kg p.o., respectively, in these animals; compound is reported to be about 5-10-fold more potent than felbamate in this test. Other exemplified felbamate derivatives include the following:



Compound	R1	R2	R3	Formula
293664	H	F	CONH2	C ₁₀ H ₁₂ FNO ₃
293666	-CONH-		CONH2	C ₁₁ H ₁₂ N ₂ O ₄
293667	-CONH-		H	C ₁₀ H ₁₁ NO ₃



293665: C10 H8 F N O3

SOURCE – University of Virginia, Charlottesville, VA (US).

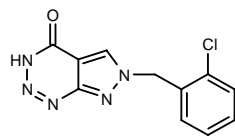
REFERENCES

1. MacDonald, T.L. et al. (University of Virginia) *Felbamate derived cpds.* WO 0047202.

AWD-34-022

293829

6-(2-Chlorobenzyl)-3,6-dihydro-4*H*-pyrazolo[3,4-*d*][1,2,3]-triazin-4-one



C11 H8 Cl N5 O; Mol wt: 261.6712

ACTION – Anticonvulsant proven to protect rats and mice against electrically induced seizures (ED₅₀ = 2.5 mg/kg p.o. in rats) and pentylenetetrazol-induced seizures (ED₅₀ = 32.4 mg/kg i.p. in mice). Moreover, compound was active in the amygdala kindling model (at 30 mg/kg) and did not induce muscle impairment at doses higher than 500 mg/kg in rats. When tested against more than 40 receptors, ion channels and second messenger systems, it was found to block only sodium channels and interact with adenosine receptors.

SOURCE – Asta Medica.

REFERENCES

1. Arnold, T. et al. (Arzneimittelwerk Dresden GmbH) *Pyrazolo[3,4-*d*][1,2,3]triazines with anticonvulsive action and methods for producing the same.* DE 19924872, WO 0073309.

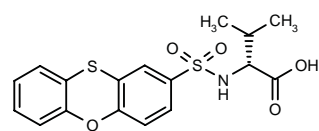
2. Lankau, A.T. et al. *Synthesis of the pyrazolotriazinone derivative AWD 33-022 and its pharmacological profile.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-133.

THERAPY OF IMMUNOLOGICAL NEUROMUSCULAR DISORDERS

293694

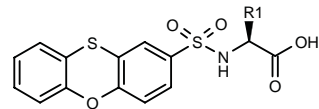
2(*R*)-3-Methyl-2-(2-Phenoxathiinylsulfonamido)butyric acid

N-(2-Phenoxathiinylsulfonyl)-D-valine



C17 H17 N O5 S2; Mol wt: 379.4553

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly stromelysin 1 (MMP-3) and gelatinase A (MMP-2), claimed for the treatment of multiple sclerosis, atherosclerotic plaque rupture, restenosis, aortic aneurysm, heart failure, periodontal disease, corneal ulceration, burns, decubital ulcers, chronic ulcers or wounds, cancer metastasis, tumor angiogenesis, osteoporosis, rheumatoid arthritis, osteoarthritis, renal disease, left ventricular dilatation and other autoimmune or inflammatory diseases dependent upon tissue invasion by leukocytes. *In vitro*, compound gave IC₅₀ values of 0.027, 0.0155, 0.27 and 0.155 μM for the catalytic domains of MMP-2, MMP-3, MMP-13 (collagenase 3) and MMP-14 (MT-1 MMP), respectively, compared to IC₅₀ values of 6.25, 19 and 12 μM for full-length MMP-1 (interstitial collagenase), MMP-7 (matrilysin) and MMP-9 (gelatinase B), respectively. Other exemplified compounds from this series of tricyclic sulfonamide derivatives include the following:



Compound	R1	Formula
293695	CH2CH2Ph	C ₂₂ H ₁₉ NO ₅ S ₂
293697	i-Pr	C ₁₇ H ₁₇ NO ₅ S ₂
293698	Me	C ₁₅ H ₁₃ NO ₅ S ₂
293701	CH2CH2SOMe	C ₁₇ H ₁₇ NO ₆ S ₃
293702	i-Bu	C ₁₈ H ₁₉ NO ₅ S ₂

SOURCE – Pfizer.

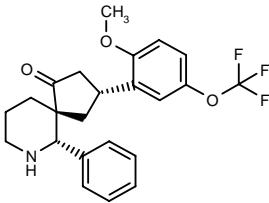
REFERENCES

1. Picard, J.A. et al. (Pfizer Inc.) *Cpds. for and methods of inhibiting matrix metalloproteinases*. US 6117869.

TREATMENT OF NAUSEA AND VOMITING

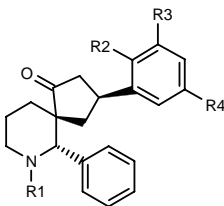
293567

(3*RS*,5*RS*,6*SR*)-3-[2-Methoxy-5-(trifluoromethoxy)-phenyl]-6-phenyl-7-azaspiro[4.5]decan-1-one

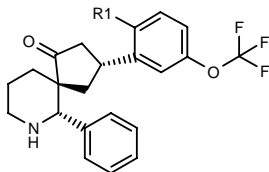


C23 H24 F3 N O3; Mol wt: 419.4406

ACTION – Potent tachykinin NK₁ receptor antagonist, potentially useful for the treatment of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety. In particular, the compound is useful for the treatment of emesis induced by cytotoxic agents. Other specifically claimed spirocyclic ketones include the following:



Compound	R1	R2	R3	R4	Formula
293568	H	cyclopropyl-O	H	OCF3	C ₂₅ H ₂₆ F ₃ NO ₃
293572	1,2,4-triazol-3-yl-CH ₂	H	Me	Me	C ₂₆ H ₃₀ N ₄ O
293573	H	OCHF2	H	OCF3	C ₂₃ H ₂₂ F ₅ NO ₃
293574	H	OCHF2	H	5-CF3-1-tetrazolyl	C ₂₄ H ₂₂ F ₅ N ₅ O ₂



Compound	R1	Formula
293569	i-PrO	C ₂₅ H ₂₈ F ₃ NO ₃
293570	cyclopropyl-CH ₂ O	C ₂₆ H ₂₈ F ₃ NO ₃
293571	OCH ₂ CF ₃	C ₂₄ H ₂₃ F ₆ NO ₃

SOURCE – Merck Sharp & Dohme.

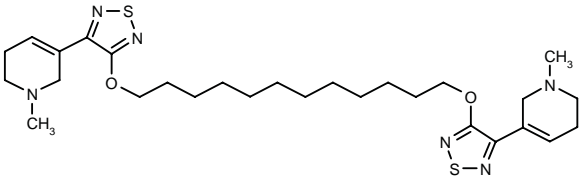
REFERENCES

1. Kulagowski, J.J. (Merck Sharp & Dohme Ltd.) *Spirocyclic ketones and their use as tachykinin antagonists*. WO 0047562.

TREATMENT OF COGNITION DISORDERS

292842

4,4'-Dodecane-1,12-diylodioxybis[5-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole]



C28 H44 N6 O2 S2; Mol wt: 560.8276

ACTION – Agent for the treatment of neurological and other disorders in which stimulating cholinergic activity is desirable such as Alzheimer's disease or pain that acts as a muscarinic M₁ receptor agonist, as demonstrated by its ability to stimulate phosphoinositol hydrolysis in A9L cells transfected with the human M₁ receptor (EC₅₀ = 0.34 μM). A specifically claimed compound from a series of bis-alkoxy-1,2,5-thiadiazole derivatives of 1,2,5,6-tetrahydropyridine.

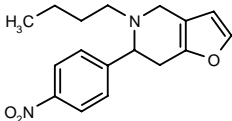
SOURCE – University of Toledo, Toledo, OH (US).

REFERENCES

1. Rajeswaran, W.G. and Messer, W.S. (University of Toledo) *Muscarinic receptor agonists*. US 6096767.

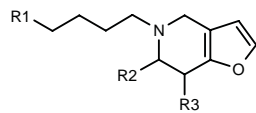
292891

5-Butyl-6-(4-nitrophenyl)-4,5,6,7-tetrahydrofuro[3,2-c]pyridine



C17 H20 N2 O3; Mol wt: 300.3560

ACTION – Neurotrophic and neuroprotective agent with potential in the treatment of neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis and memory disorders, as well as neuropathies, traumatic lesions of peripheral nerves, medulla and spinal cord, and cerebral ischemia. *In vitro*, compound exhibited concentration-dependent neuroprotective activity on differentiated PC12 cells after nerve growth factor (NGF) withdrawal. Other specifically claimed fused heterocyclic compounds are:



Compound	R1	R2	R3	Formula
292892	H	4-NH2-Ph	H	C ₁₇ H ₂₂ N ₂ O
292893	H	3-NO2-Ph	H	C ₁₇ H ₂₀ N ₂ O ₃
292894	H	3-NH2-Ph	H	C ₁₇ H ₂₂ N ₂ O
292895	H	H	Ph	C ₁₇ H ₂₁ NO
292896	Et	H	H	C ₁₃ H ₂₁ NO

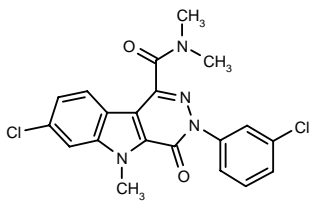
SOURCE – NeuroSearch.

REFERENCES

1. Peters, D. et al. (NeuroSearch A/S) *Fused heterocyclic cpds. and their use in the treatment of neurodegenerative diseases.* WO 0043397.

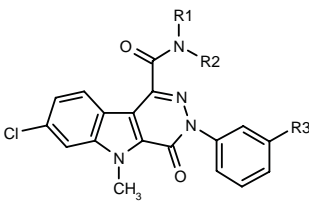
293072

7-Chloro-3-(3-chlorophenyl)-N,N,5-trimethyl-4-oxo-4,5-dihydro-3H-pyridazino[4,5-b]indole-1-carboxamide



C20 H16 Cl2 N4 O2; Mol wt: 415.2784

ACTION – Agent with affinity for peripheral benzo-diazepine receptors and neurotrophic activity, with potential for the treatment or prevention of peripheral neuropathies, as well as amyotrophic lateral sclerosis and acute and chronic neurodegenerative disorders such as stroke or Alzheimer’s disease. Other exemplified compounds from this series of 4-oxo-3,5-dihydro-4H-pyridazino[4,5-b]indole-1-carboxamide derivatives include the following:



Compound	R1	R2	R3	Formula
293073	Me	Me	H	C ₂₀ H ₁₇ ClN ₄ O ₂
293074	-(CH2)4-		Cl	C ₂₂ H ₁₈ Cl ₂ N ₄ O ₂
293075	Me	Me	F	C ₂₀ H ₁₆ ClFN ₄ O ₂

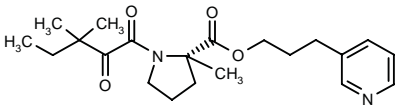
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Marguet, F. et al. (Sanofi-Synthélabo) *4-Oxo-3,5-dihydro-4H-pyridazino[4,5-b]indole-1-carboxamide derivs., preparation and therapeutic use.* FR 2788776, WO 0044751.

293349

1-(3,3-Dimethyl-2-oxopentanoyl)-2(S)-methylpyrrolidine-2-carboxylic acid 3-(3-pyridyl)propyl ester



C21 H30 N2 O4; Mol wt: 374.4780

ACTION – Neurotrophic agent for the treatment or prevention of neurodegenerative diseases, for stimulating neuronal regeneration, as well as for stimulating neurite growth, a specifically claimed compound from a series of carboxylic acid derivatives that are believed to act by increasing cytoplasmic Ca²⁺ concentrations through an interaction with a calcium release channel such as the ryanodine receptor or the Ins(1,4,5)P₃ receptor in the endoplasmic reticulum of the nerve cell. It is devoid of affinity for FK-506-binding protein (FKBP) and multidrug resistance (MDR)-reversing activity, contrary to previously reported compounds.

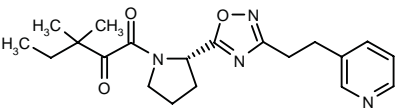
SOURCES – Schering AG; Vertex.

REFERENCES

1. Brumby, T. et al. (Schering AG;Vertex Pharmaceuticals Inc.) *Carboxylic acid derivs., process for their preparation and their use as rotamase enzyme activity inhibitors.* DE 19905255, WO 0046181.

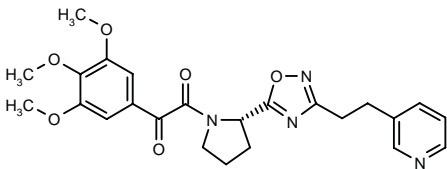
293350

3,3-Dimethyl-1-[2(S)-[3-[2-(3-pyridyl)ethyl]-1,2,4-oxadiazol-5-yl]pyrrolidin-1-yl]pentane-1,2-dione



C20 H26 N4 O3; Mol wt: 370.4504

ACTION – Neurotrophic agent for the treatment or prevention of neurodegenerative diseases, for stimulating neuronal regeneration, as well as for stimulating neurite growth, a representative compound from a series of heteroaromatic derivatives that are believed to act by increasing cytoplasmic Ca²⁺ concentrations through an interaction with a calcium release channel such as ryanodine receptors or Ins(1,4,5)P₃ receptors in the endoplasmic reticulum of the nerve cell, and which are devoid of affinity for FK-506-binding protein (FKBP) and multidrug resistance (MDR)-reversing activity, contrary to previously reported compounds. Another specifically claimed compound is:



293351: C24 H26 N4 O6

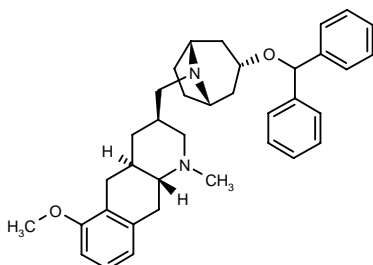
SOURCES – Schering AG; Vertex.

REFERENCES

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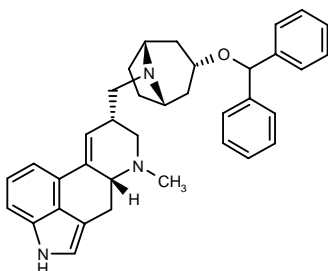
293360

(3*S*,4*aR*,10*aR*)-3-[*endo*-3-(Diphenylmethoxy)-8-azabicyclo[3.2.1]oct-8-ylmethyl]-6-methoxy-1-methyl-1,2,3,4,4*a*,5,10,10*a*-octahydrobenzo[*g*]quinoline



C36 H44 N2 O2; Mol wt: 536.7556

ACTION – Agent for the treatment of amyloidoses such as Alzheimer's disease, Down's syndrome, multiinfarct dementia and cerebral hemorrhage with amyloidosis that acts by inhibiting the formation of β -amyloid peptide into neurotoxic fibrils, thereby acting to prevent or slow down the accumulation of amyloid protein deposits in the brain. Another specifically claimed compound from this series of piperidine and piperazine derivatives is:



293361: C36 H39 N3 O

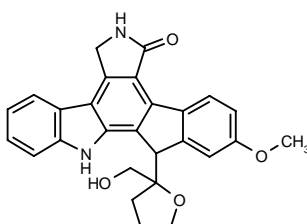
SOURCE – Novartis.

REFERENCES

1. Lüönd, R.M. et al. (Novartis AG) *Piperidine and piperazine derivs. as inhibitors of the A β fibril formation*. WO 0047571.

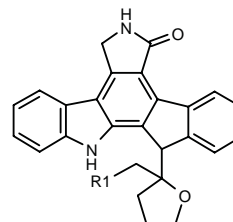
293686

13-(2-Hydroxymethyltetrahydrofuran-2-yl)-2-methoxy-6,7,12,13-tetrahydro-5*H*-indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazol-5-one



C27 H24 N2 O4; Mol wt: 440.4966

ACTION – Agent for enhancing trophic factor-induced activities of trophic factor-responsive cells, e.g., cholinergic neurons, as well as for promoting the survival of other neuronal cell types, e.g., dopaminergic and glutamatergic cells; it also inhibits kinases such as trkA kinase (IC_{50} = 8 nM), vascular endothelial growth factor (VEGF) receptor kinase (IC_{50} = 209 nM) and, to a lesser extent, protein kinase C (IC_{50} = 2205 nM). *In vitro*, compound was also shown to inhibit nerve growth factor (NGF)-stimulated trk phosphorylation in NIH3T3 cells (76-100% inhibition at 100 nM). Potentially useful for the treatment or prevention of Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, stroke, Huntington's disease, ischemia, epilepsy, multiple sclerosis, peripheral neuropathy or brain or spinal cord injury, as well as cancer, benign prostatic hyperplasia, rheumatoid arthritis, pulmonary fibrosis, atherosclerosis, restenosis, endometriosis, psoriasis and ocular disorders. Other exemplified compounds from this series of cyclic substituted fused pyrrolocarbazoles and isoindolones include the following:



Compound	R1	Formula
293687	H	C ₂₆ H ₂₂ N ₂ O ₂
293688	OH	C ₂₆ H ₂₂ N ₂ O ₃
293690	t-BuCOO	C ₃₁ H ₃₀ N ₂ O ₄

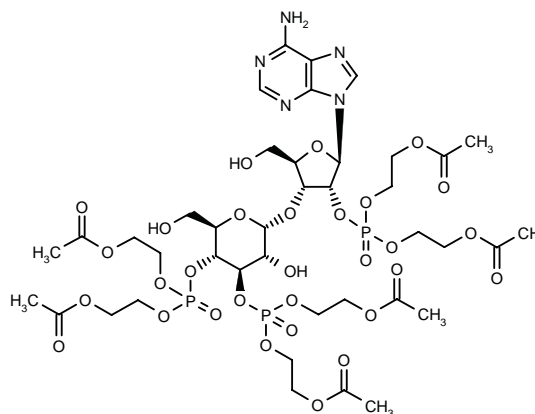
SOURCE – Cephalon.

REFERENCES

1. Hudkins, R.L. et al. (Cephalon, Inc.) *Cyclic subst. fused pyrrolocarbazoles and isoindolones*. WO 0047583.

293878

2'-*O*-[Bis(2-acetoxyethoxy)phosphoryl]-3'-*O*-[3,4-*O*-bis[bis(2-acetoxyethoxy)phosphoryl]- β -D-glucopyranosyl]-adenosine



C40 H62 N5 O30 P3; Mol wt: 1185.8570

ACTION – A representative compound from a series of phosphoric acid derivatives that act by increasing intracellular calcium ion (Ca^{2+}) concentrations and are thus expected to be useful in the treatment of neurological disorders such as Alzheimer's disease, senile dementia and Huntington's chorea, as well as for the treatment of ulcers, type 1 diabetes and for use as vasopressor or immunopotentiating agents.

SOURCE – Sankyo.

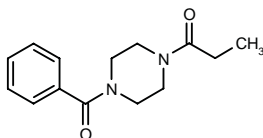
REFERENCES

1. Hotoda, H. et al. (Sankyo Co., Ltd.) *Phosphoric acid derivs.* JP 2000212191.

DM-235

293597

1-(4-Benzoylpiperazin-1-yl)propan-1-one



C14 H18 N2 O2; Mol wt: 246.3082

ACTION – Nootropic agent for the treatment of Alzheimer's disease or senile dementia, proven to prevent amnesia induced by scopolamine in a rat passive avoidance test with a minimal effective dose (MED) of 0.001 mg/kg s.c. and 0.1 mg/kg p.o., as well as by other amnesic agents (clonidine, mecamylamine, baclofen, diphenhydramine). Moreover, compound was able to improve cognitive performance in a social learning test in rats. No impairment of motor coordination or spontaneous motility was seen at doses 1,000-fold higher than the MED for preventing amnesia. Although the molecular mechanism remains to be elucidated, the compound is able to increase acetylcholine release from rat cerebral cortex at a dose of 0.01 mg/kg i.p., and it possesses atropine-sensitive analgesic activity, as demonstrated in the mouse hot-plate test.

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

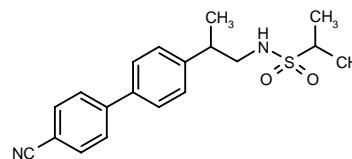
1. Manetti, D. et al. *1,4-Diazabicyclo[4.3.0]nonan-9-ones and 1,4-diamidopiperazines as new classes of highly potent nootropic drugs.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-119.

2. Mannetti, D. et al. *Molecular simplification of 1,4-diazabicyclo[4.3.0]nonan-9-ones gives piperazine derivatives that maintain high nootropic activity.* J Med Chem 2000, 43(23): 4499.

LY-404187^{1,4,6-8}

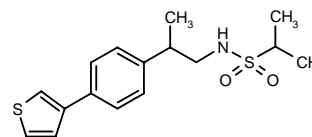
293600

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]propane-2-sulfonamide



C19 H22 N2 O2 S; Mol wt: 342.4608

ACTION – Cognition-enhancing agent proven to potentiate glutamate-induced ion influx through recombinant monomeric human AMPA receptor channel subtypes GluR1-4 (EC_{50} = 1.94, 0.15, 1.52 and 0.17 μM for GluR1, GluR2, GluR3 and GluR4, respectively), without affecting ion influx in the absence of agonist. Compound was seen to potentiate glutamate-evoked inward currents in both human HEK293 cells expressing human GluR4 receptors and isolated cerebellar Purkinje neurons, as well as AMPA-induced currents in cultured rat hippocampal neurons. Compound administered systemically to rats was able to potentiate central AMPA receptor functions at doses similar to those that cause behavioral changes. In rats with age-associated memory deficits, it reversed memory deficits at doses ranging from 0.01 to 1 mg/kg p.o. Another related compound is:



LY-392098 [293601]:^{1,2,4-9} C16 H21 N O2 S2

SOURCE – Lilly.

REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) *N-Substd. sulfonamide derivs.* WO 0006537.

2. Arnold, M.B. et al. (Eli Lilly and Company) *Sulphonamide derivs.* EP 0860428, WO 9833496.

3. Baumbarger, P.J. et al. *Positive modulation of AMPA receptors in prefrontal cortical neurons by a novel allosteric potentiator: In vitro and in vivo studies.* Soc Neurosci Abst 2000, 26(Part 1): Abst 339.20.

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5. Clark, A.G. et al. *Electrophysiological effects of AMPA receptor modulators on cultured hippocampal neurons and HEK293 cells expressing non-desensitising GluR1 and GluR3.* Soc Neurosci Abst 2000, 26(Part 1): Abst 339.14.

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7. Ornstein, P.L. *Structurally novel AMPA potentiators: New opportunities for drug development.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst ML-51.

8. Ornstein, P.L. et al. *Biarylpropylsulfonamides as novel, potent potentiators of 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid (AMPA) receptors.* J Med Chem 2000, 43(23): 4354.

9. Zhai, Y. et al. *The novel AMPA receptor potentiator, LY 392098 enhances c-fos expression in limbic forebrain regions of the rat.* Soc Neurosci Abst 2000, 26 (Part 1): Abst 339.22.

TREATMENT OF ATTENTION DEFICIT
HYPERACTIVITY DISORDER

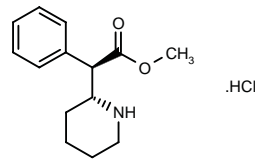
OROS®-METHYLPHENIDATE *New formulation*
280367

Once-daily extended-release formulation using OROS® osmotic technology to deliver methylphenidate hydrochloride

Methylphenidate hydrochloride

282606

(±)-(R*,R*)-2-Phenyl-2-(2-piperidiny)acetic acid methyl ester hydrochloride



C14 H19 N O2 . HCl ; Mol wt: 269.7700

ACTION – New once-daily, extended-release formulation using the OROS® drug delivery system of a central nervous system stimulant thought to act by blocking norepinephrine and dopamine reuptake into presynaptic neurons and increasing the release of these monoamines into the extraneuronal space.

INDICATIONS – Treatment of attention deficit hyperactivity disorder in patients age 6 and older.

PRESENTATION – Extended-release tablets, 18, 36 and 54 mg.

PROPRIETARY NAME – Concerta (US).

SOURCES – Alza; copromoted by McNeil Consumer Healthcare.

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1. Bao, F. et al. *Desiccant compatibility study for OROS® (methylphenidate HCl) tablets.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3077.

2. Chaturvedi, K. and Chang, K. *Evaluation of an automated Vankel Biodis tester for release-rate testing of ALZA OROS® (methylphenidate HCl) formulations.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3367.

3. Greenhill, L.L. *Evaluation of the efficacy and safety of Concerta (methylphenidate HCl) extended release tablets, Ritalin, and placebo in children with ADHD.* Neurology 2000, 54(7, Suppl. 3): Abst P06.049.

4. Modi, N.B. and Gupta, S.K. *Clinical pharmacokinetics of a once-a-day, osmotic, controlled-release methylphenidate formulation (Concerta™) for treating children with ADHD.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.15.05.

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12. *Alza's 1998 milestones, priorities for 1999.* DailyDrugNews.com (Daily Essentials) 1999, Feb 19.

13. *Concerta approved by FDA, licensed worldwide by Alza.* DailyDrugNews.com (Daily Essentials) 2000, Aug 3.

14. *Concerta to be copromoted by Alza and McNeil for ADD/ADHD.* DailyDrugNews.com (Daily Essentials) 2000, May 16.

15. *Favorable safety and efficacy data reported for Concerta; FDA issues approvable letter.* DailyDrugNews.com (Daily Essentials) 2000, May 29.

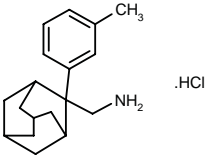
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TREATMENT OF
CEREBROVASCULAR DISEASES

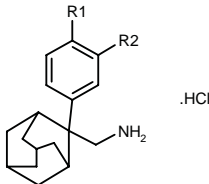
293033

1-[2-(3-Methylphenyl)adamantan-2-yl]methylamine hydrochloride



C18 H25 N . HCl; Mol wt: 291.8634

ACTION – NMDA antagonist for the treatment of disorders of glutamatergic transmission including stroke, traumatic brain injury and neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. Results from *in vitro* assays using rat cortical and cerebellar membranes demonstrated that this compound has a favorable ratio of cortical to cerebellar NMDA receptor binding affinity (IC₅₀ = 13 and 6 μM, respectively), indicating that it may be well tolerated *in vivo*. Other specifically claimed 2-adamantanemethanamide compounds are:



Compound	R1	R2	Formula
293034	H	Et	C ₁₉ H ₂₇ N.HCl
293035	H	H	C ₁₇ H ₂₃ N.HCl
293037	Me	H	C ₁₈ H ₂₇ N.HCl

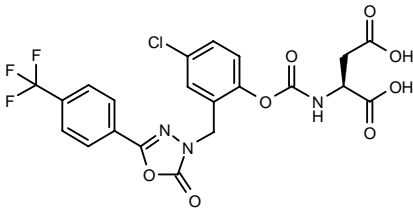
SOURCE – Vernalis Research.

REFERENCES

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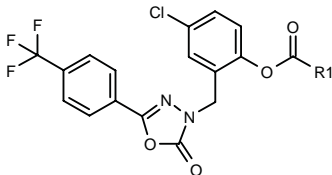
293102

N-[4-Chloro-2-[2-oxo-5-(4-trifluoromethylphenyl)-2,3-dihydro-1,3,4-oxadiazol-3-ylmethyl]phenoxy-carbonyl]-L-aspartic acid



C21 H15 Cl F3 N3 O8; Mol wt: 529.8095

ACTION – Carbamate derivative of a known* opener of large-conductance Ca²⁺-activated K⁺ (BK_{Ca}) channels that acts as a water-soluble prodrug of the latter. Preferably, this prodrug is useful for the treatment of cerebral ischemia. Other specifically claimed prodrugs are:



Compound	R1	Formula
293103	-L-Ala-OH	C ₂₀ H ₁₅ ClF ₃ N ₃ O ₆
293104	-L-Glu-OH	C ₂₂ H ₁₇ ClF ₃ N ₃ O ₈
293105	-L-Leu-OH	C ₂₃ H ₂₁ ClF ₃ N ₃ O ₆
293106	NHCH ₂ CH ₂ N(Me) ₂	C ₂₁ H ₂₀ ClF ₃ N ₄ O ₄
293107	N(Me)CH ₂ CH ₂ N(Me) ₂	C ₂₂ H ₂₂ ClF ₃ N ₄ O ₄
293108	4-Me-1-Piz	C ₂₂ H ₂₀ ClF ₃ N ₄ O ₄
293109	4-morpholinyl-CH ₂ CH ₂ NH	C ₂₃ H ₂₂ ClF ₃ N ₄ O ₅

SOURCE – Bristol-Myers Squibb.

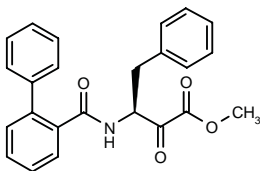
REFERENCES

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*See 272624 Drug Data Rep 1999, 021(03): 0214.

293238

3(*S*)-(Biphenyl-2-ylcarboxamido)-2-oxo-4-phenylbutyric acid methyl ester



C24 H21 N O4; Mol wt: 387.4329

ACTION – An inhibitor of cysteine proteases such as calpain I and/or II and cathepsin B and/or L, potentially useful for the treatment of neurodegenerative disorders following ischemia, trauma, subarachnoid hemorrhage and stroke, neurodegenerative disorders such as Alzheimer’s disease and Huntington’s disease, as well as cardiac or renal ischemia, rheumatoid arthritis, muscular dystrophy, restenosis, coronary or cerebral vasospasm, cataracts and cancer. A representative compound from a series of ketobenzamides.

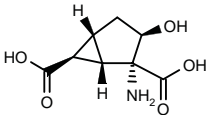
SOURCE – BASF.

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293304

(1*S*,2*R*,3*R*,5*R*,6*S*)-2-Amino-3-hydroxybicyclo[3.1.0]-hexane-2,6-dicarboxylic acid



C8 H11 N O5; Mol wt: 201.1769

ACTION – Group II metabotropic glutamate receptor antagonist, as demonstrated by K_i values of 0.052 and 0.089 μM in receptor binding assays using rat mglu₂ and mglu₃ receptors, respectively. Potentially useful for the treatment of acute and chronic neurological conditions and psychiatric disorders. A specifically claimed compound from a series of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives.

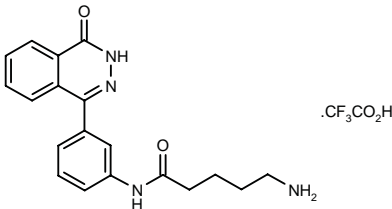
SOURCE – Roche.

REFERENCES

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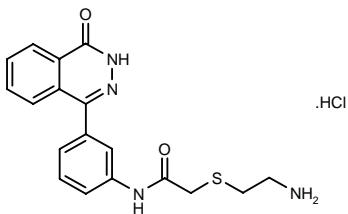
293311

5-Amino-*N*-[3-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl]-pentanamide trifluoroacetate

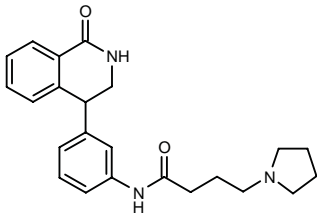


C19 H20 N4 O2 . C2 H F3 O2; Mol wt: 450.4149

ACTION – PARP (poly[ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase) inhibitor (IC₅₀ = 42 nM), potentially useful for the treatment or prevention of ischemic disorders, inflammatory diseases, neurodegenerative diseases, diabetes, shock, head trauma, renal insufficiency, hyperalgesia and cancer. Other exemplified compounds from this series of 2*H*-phthalazin-1-one derivatives include the following:



293313: C18 H18 N4 O2 S . HCl



293314: C23 H27 N3 O2

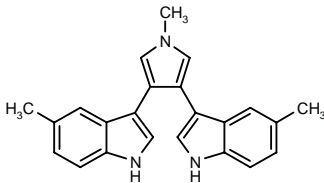
SOURCE – Ono.

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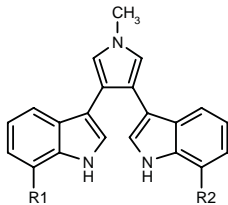
293492

1-Methyl-3,4-bis(5-methyl-1*H*-indol-3-yl)-1*H*-pyrrole



C23 H21 N3; Mol wt: 339.4399

ACTION – Apoptosis inhibitor with a minimum effective concentration (MEC) of 0.05 μ M for inhibition of sodium nitroprusside-induced apoptosis in porcine ovarian granulosa cells. In addition, compound was shown to inhibit apoptosis of rat granulosa cells induced by bilirubin, sodium azide, antimycin A, glutamic acid and FCCP at 10 μ M, with cell viability of > 95%, and it potently inhibited H₂O₂-induced hemolysis of human erythrocytes at 5 μ M. Other exemplified compounds from this series of pyrrole derivatives include the following:



Compound	R1=R2	Formula
293493	H	C ₂₁ H ₁₇ N ₃
293494	Me	C ₂₃ H ₂₁ N ₃

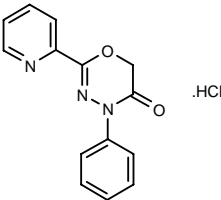
SOURCE – Sagami.

REFERENCES

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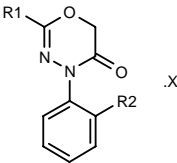
293730

4-Phenyl-2-(2-pyridyl)-5,6-dihydro-4*H*-1,3,4-oxadiazin-5-one hydrochloride



C14 H11 N3 O2 . HCl; Mol wt: 289.7208

ACTION – AMPA receptor antagonist with potential for the treatment of acute and chronic neurodegenerative diseases, epilepsy, pain and demyelinating diseases. *In vitro*, compound inhibited AMPA-induced calcium uptake and AMPA-induced current in rat astrocytes with IC₅₀ values of 11.8 and 12.3 μ M, respectively. *In vivo*, it exhibited significant neuroprotective activity, inhibiting spasms induced by intracerebroventricular administration of AMPA in mice (80% inhibition or greater at 30 mg/kg i.v.) and reducing infarct area in rats subjected to middle cerebral artery occlusion (54 and 74% reduction at 6.6 mg/kg i.v. bolus + 10 mg/kg/h i.v. and 20 mg/kg i.v. bolus + 30 mg/kg/h i.v., respectively). Other compounds from this series of heterodiazinone derivatives include the following:



Compound	R1	R2	X	Formula
293732	3-OH-2-Pyr	H		C ₁₄ H ₁₁ N ₃ O ₃
293733	Ph	CN		C ₁₆ H ₁₁ N ₃ O ₂
293734	2-[N(Me)2CH2CH2O]-Ph	Br	HCl	C ₁₉ H ₂₀ BrN ₃ O ₃ .HCl
293736	2-(4-morpholinyl-CH2CH2O)-Ph	Br	HCl	C ₂₁ H ₂₂ BrN ₃ O ₄ .HCl

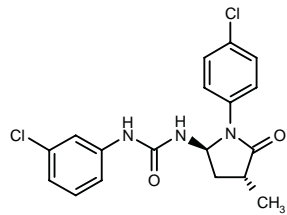
SOURCE – Eisai.

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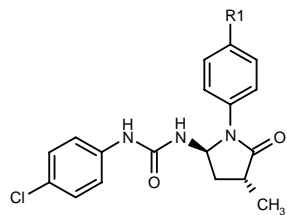
293795

trans-*N*-(3-Chlorophenyl)-*N*'-[1-(4-chlorophenyl)-4-methyl-5-oxopyrrolidin-2-yl]urea



C18 H17 Cl2 N3 O2; Mol wt: 378.2573

ACTION – Agent for the treatment of neurological and CNS disorders such as stroke, schizophrenia, Alzheimer’s disease, senile dementia, vascular dementia and depression, an inhibitor of glutamic acid uptake (IC₅₀ = 6.6 μM in rat brain synaptosomes). Other exemplified compounds from this series of phenyl pyrrolidinone derivatives include the following:



Compound	R1	Formula
293796	Cl	C ₁₈ H ₁₇ Cl ₂ N ₃ O ₂
293798	F	C ₁₈ H ₁₇ ClFN ₃ O ₂

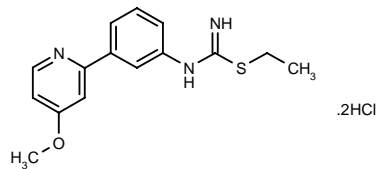
SOURCE – Eisai.

REFERENCES

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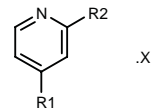
293802

S-Ethyl-*N*-[3-(4-methoxypyridin-2-yl)phenyl]isothiurea dihydrochloride



C15 H17 N3 O S . 2HCl; Mol wt: 360.3071

ACTION – Nitric oxide synthase (NOS) inhibitor (100% inhibition of enzyme from rat brain at 100 μM), with potential for the treatment or prevention of NOS-mediated diseases such as adult respiratory distress syndrome, myocarditis, synovitis, septic shock, insulin-dependent diabetes mellitus, ulcerative colitis, cerebral infarction, rheumatoid arthritis, osteoarthritis, osteoporosis, systemic lupus erythematosus, transplant organ rejection, asthma, pain and ulcers. Other compounds from this series of pyridine derivatives include the following:



Compound	R1	R2	X	Formula
293806	OMe	4-Me-2-[NH2C(=NH)NH]-5-thiazolyl		C ₁₁ H ₁₃ N ₅ OS
293809	OMe	4-Me-3-[NH2C(=NH)NH]-Ph	2HCl	C ₁₄ H ₁₆ N ₄ O.2HCl
293813	OMe	2-NH-7-quinolyl	2HCl	C ₁₅ H ₁₃ N ₃ O.2HCl
293814	Me	2-NH-7-quinolyl	2HCl	C ₁₅ H ₁₃ N ₃ .2HCl
293815	OMe	2-(MeNH)-7-quinolyl	2HCl	C ₁₆ H ₁₅ N ₃ O.2HCl

SOURCE – Fujisawa.

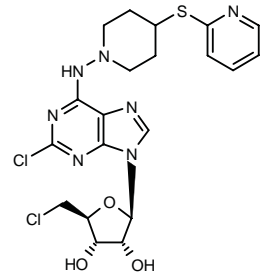
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NNC-21-0300^{1,2}

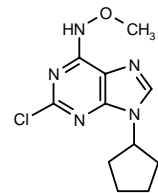
293512

5'-Deoxy-2,5'-dichloro-*N*⁶-[4-(2-pyridylsulfanyl)piperidin-1-yl]adenosine



C20 H23 Cl2 N7 O3 S; Mol wt: 512.4197

ACTION – Selective adenosine A₁ receptor agonist, an adenosine analogue endowed with neuroprotective effects in models of focal and global cerebral ischemia while exerting mild cardiovascular effects in anesthetized rats. Another modified adenosine analogue is the selective A₃ receptor agonist **NNC-53-0016**, which also exhibits potent inhibition of TNF-α and phosphodiesterase type 4 (PDE4).



NNC-53-0016 [293514]:² C11 H14 Cl N5 O

SOURCE – Novo Nordisk.

REFERENCES

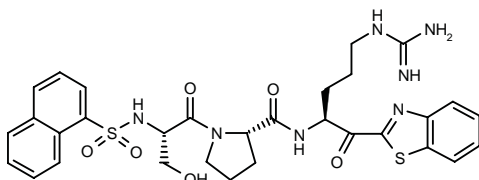
1. Knutsen, L. (Novo Nordisk A/S) *Novel therapeutically active adenosine derivs.* WO 9816539.
2. Knutsen, L.J.S. et al. *New ligands at adenosine (P1) receptors.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst ML-28.

RESPIRATORY DRUGS

ASTHMA THERAPY

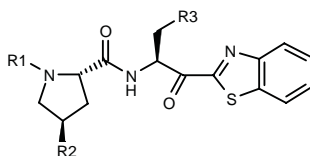
293076

2-[N-(1-Naphthylsulfonyl)-L-seryl-L-prolyl-L-arginyl]-benzothiazole



C31 H35 N7 O6 S2; Mol wt: 665.7925

ACTION – Potent and selective tryptase inhibitor (IC_{50} = 0.014 ± 0.005 and 0.058 ± 0.012 μ M, respectively, against tryptase and trypsin), potentially useful for the treatment of immune-mediated inflammatory disorders, particularly those mediated by mast cells such as asthma, as well as trypsin-mediated disorders such as pancreatitis. Other exemplified peptidyl heterocyclic ketones include the following:



Compound	R1	R2	R3	Formula
293079	Ac	OH	CH ₂ CH ₂ NH-C(=NH)NH ₂	C ₂₀ H ₂₆ N ₆ O ₄ S
293082	N(CH ₂ CO ₂ H)-3-cyclohexyl-D-Ala-	H	CH ₂ CH ₂ NH-C(=NH)NH ₂	C ₂₉ H ₄₁ N ₇ O ₅ S
293085	N-Me-D-Phe-	H	(R)-1-[NH ₂ -C(=NH)]-3-Pip	C ₃₁ H ₃₉ N ₇ O ₅ S

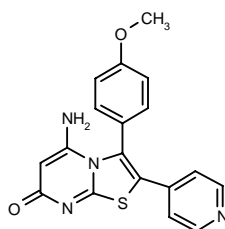
SOURCE – Ortho-McNeil.

REFERENCES

1. Costanzo, M.J. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Peptidyl heterocyclic ketones useful as tryptase inhibitors*. WO 0044733.

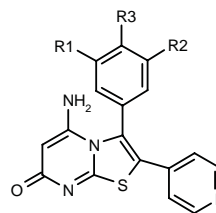
293120

5-Amino-3-(4-methoxyphenyl)-2-(4-pyridinyl)-7H-thiazolo[3,2-a]pyrimidin-7-one



C18 H14 N4 O2 S; Mol wt: 350.4006

ACTION – Potent human adenosine A₃ receptor antagonist (IC_{50} = 3.5 nM), expected to be useful for the treatment of asthma, allergic diseases, cerebrovascular disorders, brain injury and brain edema. Other exemplified thiazolopyrimidine compounds are:



Compound	R1=R2	R3	Formula
293121	H	t-Bu	C ₂₁ H ₂₀ N ₄ OS
293122	Me	H	C ₁₉ H ₁₆ N ₄ OS

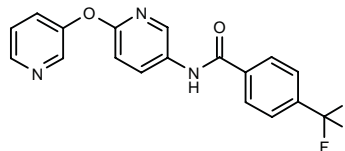
SOURCE – Takeda.

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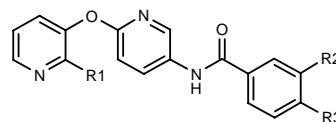
293159

N-[6-(3-Pyridinyloxy)pyridin-3-yl]-4-(trifluoromethyl)-benzamide



C18 H12 F3 N3 O2; Mol wt: 359.3058

ACTION – Agent that interacts with G-protein-coupled heptahelical receptors, particularly β -chemokine receptors such as CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8 and CCR10, with potential for the treatment of chemokine-mediated disorders such as neurological, immunological and inflammatory disorders and cancer. *In vitro*, compound, exhibited high binding affinity for the CCR10 receptor expressed in K293 cells and was shown to concentration-dependently block MCP-1- or MCP-3-induced migration of THP-1 cells expressing both CCR10 and CCR2 receptors. *In vivo*, it significantly reduced MCP-5-induced peritoneal eosinophil recruitment in mice when given at 50 nmol/kg i.v. 30 min prior to MCP-5 administration. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
293161	Me	H	CF ₃	C ₁₉ H ₁₄ F ₃ N ₃ O ₂
293162	H	H	Cl	C ₁₇ H ₁₂ ClN ₃ O ₂
293163	Me	F	CF ₃	C ₁₉ H ₁₃ F ₄ N ₃ O ₂
293164	Me	H	I	C ₁₈ H ₁₄ I ₃ N ₃ O ₂

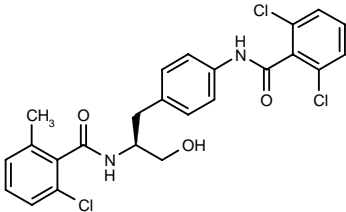
SOURCE – Millennium.

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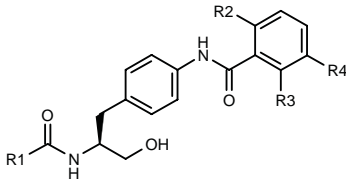
293766

N-(2-Chloro-6-methylbenzoyl)-4-(2,6-dichlorobenzamido)-L-phenylalaninol



C24 H21 Cl3 N2 O3; Mol wt: 491.7999

ACTION – An inhibitor of the binding of VCAM-1 and fibronectin to VLA-4, potentially useful in the treatment of chronic inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma and inflammatory bowel disease. Other specifically claimed compounds from this series of phenylalaninol derivatives are:



Compound	R1	R2	R3	R4	Formula
293767	2-Br-Ph	Cl	Cl	H	C ₂₃ H ₁₉ BrCl ₂ N ₂ O ₃
293768	1-[MeSO ₂ (CH ₂) ₄]-1-cyclopentyl	Me	H	NO ₂	C ₂₈ H ₃₇ N ₃ O ₇ S
293769	1-[MeSO ₂ (CH ₂) ₄]-1-cyclopentyl	Me	Me	H	C ₂₉ H ₄₀ N ₂ O ₅ S
293770	1-[MeSO ₂ (CH ₂) ₄]-1-cyclopentyl	CF ₃	H	H	C ₂₈ H ₃₅ F ₃ N ₂ O ₅ S
293771	1-[MeS(CH ₂) ₄]-1-cyclopentyl	Me	H	NO ₂	C ₂₈ H ₃₇ N ₃ O ₅ S
293772	1-[MeSO ₂ (CH ₂) ₃]-1-cyclopentyl	Cl	Cl	H	C ₂₆ H ₃₂ Cl ₂ N ₂ O ₅ S
293774	1-(MeOCH ₂ CH ₂)-1-cyclopentyl	Cl	Cl	H	C ₂₅ H ₃₀ Cl ₂ N ₂ O ₄
293775	1-[MeSO ₂ (CH ₂) ₄]-1-cyclopentyl	Cl	Cl	H	C ₂₇ H ₃₄ Cl ₂ N ₂ O ₅ S
293776	2-Br-Ph	Me	Me	H	C ₂₅ H ₂₅ BrN ₂ O ₃

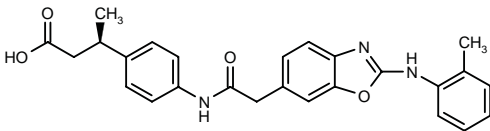
SOURCE – Roche.

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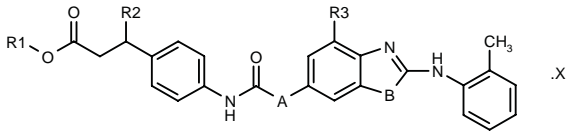
293972

3(*R*)-[4-[2-[2-(2-Methylphenylamino)benzoxazol-6-yl]-acetamido]phenyl]butyric acid



C26 H25 N3 O4; Mol wt: 443.5005

ACTION – An inhibitor of the interaction of VCAM-1 and fibronectin with the integrin receptor VLA-4 ($\alpha_4\beta_1$), with potential in the treatment of diseases mediated by $\alpha_4\beta_1$ -regulated cell adhesion such as asthma, inflammatory diseases and inflammatory bowel disease. Other exemplified bicyclic compounds include the following:



Compound	R1	R2	R3	A	B	X	Formula
293973	H	(R)-Me	H	-CH ₂ -	NH	2H ₂ O	C ₂₆ H ₂₆ N ₄ O ₃ .2H ₂ O
293975	H	(R)-Me	OMe	-CH ₂ -	O		C ₂₇ H ₂₇ N ₃ O ₅
293976	H	(R)-Me	Me	-CH ₂ -	O		C ₂₇ H ₂₇ N ₃ O ₄
293977	H	Ph	H	-CH ₂ -	O		C ₃₁ H ₂₇ N ₃ O ₄
293978	H	(R)-Me	H	-(CH ₂) ₂ -	O		C ₂₇ H ₂₇ N ₃ O ₄
293979	H	(CH ₂) ₃ OH	H	-CH ₂ -	O		C ₂₈ H ₂₉ N ₃ O ₅
293980	Li	(CH ₂) ₃ OH	H	-CH ₂ -	NH	CF ₃ CO ₂ H	C ₂₈ H ₂₉ LiN ₄ O ₄ .C ₂ HF ₃ O ₂

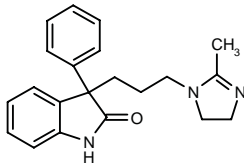
SOURCE – Aventis Pharma.

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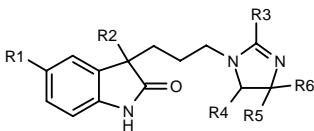
293983

3-[3-(2-Methyl-4,5-dihydro-1*H*-imidazol-1-yl)propyl]-3-phenyl-2,3-dihydro-1*H*-indol-2-one



C21 H23 N3 O; Mol wt: 333.4327

ACTION – Selective muscarinic M₃ receptor antagonist with pA₂ values of 8.4, 8.2 and 8.2 when tested *in vitro* for its ability to inhibit carbachol-induced contractions in M₃-bearing tissues, i.e., guinea pig trachea, bladder and ileum, respectively; its affinity for M₂ receptors was lower, as demonstrated in guinea pig left atrial preparations (pA₂ = 7.5). *In vivo*, it exhibited marked activity in inhibiting methacholine-induced bronchoconstriction in guinea pigs, with ID₅₀ values of 0.9 µg/kg i.v. and 11.8 µg/ml by inhalation, while it showed an ID₅₀ value of 3.2 µg/kg i.v. for inhibition of oxotremorine-induced salivary secretion in the rat. Other exemplified compounds from this series of cyclic amide derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
293984	H	Ph	Me	bond		H	C ₂₁ H ₂₁ N ₃ O
293985	H	3-Me-Ph	Me	H	H	H	C ₂₂ H ₂₅ N ₃ O
293986	Me	Ph	Me	H	H	H	C ₂₂ H ₂₅ N ₃ O
293987	H	cyclopentyl	Me	H	H	H	C ₂₀ H ₂₇ N ₃ O
293988	H	Ph	H	H	Me	Me	C ₂₂ H ₂₅ N ₃ O

SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

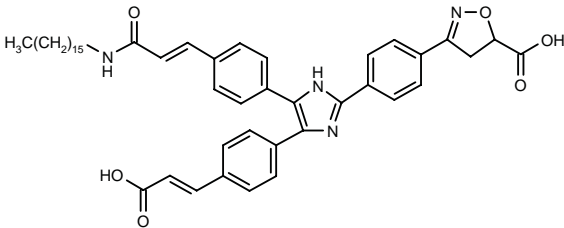
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OC-229-648

293974

3-[4-[4-[4-[(E)-2-Carboxyvinyl]phenyl]-5-[4-[(E)-3-(hexadecylamino)-3-oxo-1-propenyl]phenyl]-1 H-imidazol-2-yl]phenyl]-4,5-dihydroisoxazole-5-carboxylic acid



C47 H56 N4 O6; Mol wt: 772.9814

ACTION – Noncarbohydrate, small-molecule selectin inhibitor (IC₅₀ = 300 nM against P-selectin) able to inhibit both P- and E-selectin-mediated cell adhesion (IC₅₀ = 10-30 μM). Compound was found to reduce leukocyte rolling on vascular endothelium and exhibited antiinflammatory activity *in vivo*, attenuating both irritant-induced peritonitis and delayed-type hypersensitivity in mice. Good water solubility was seen and significant blood levels were maintained for several hours after i.v. administration. Currently undergoing efficacy studies in sheep models of asthma and chronic obstructive pulmonary disease.

SOURCES – Ontogen; Organon.

REFERENCES

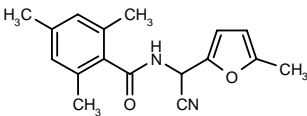
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2. Romano, S.J. et al. *OC229-648, a novel, non-carbohydrate small molecule selectin inhibitor with anti-inflammatory activity.* Inflamm Res 2000, 49(Suppl. 2): S90.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

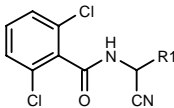
293691

N-[1-Cyano-1-(5-methylfuran-2-yl)methyl]-2,4,6-trimethylbenzamide



C17 H18 N2 O2; Mol wt: 282.3412

ACTION – Cysteine protease, particularly cathepsin L and/or S, inhibitor proven active in standard *in vitro* tests for inhibition of human and rabbit cathepsin L. Potentially useful for the treatment of chronic obstructive pulmonary disease. Other exemplified acylated aminoacetonitriles include the following:



Compound	R1	Formula
293692	OMe	C ₁₀ H ₈ Cl ₂ N ₂ O ₂
293693	NHAc	C ₁₁ H ₉ Cl ₂ N ₃ O ₂

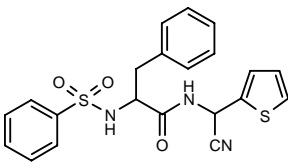
SOURCE – AstraZeneca.

REFERENCES

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293817

N¹-[1-Cyano-1-(2-thienyl)methyl]-N²-(phenylsulfonyl)-DL-phenylalaninamide



C21 H19 N3 O3 S2; Mol wt: 425.5311

ACTION – An inhibitor of cysteine proteases, particularly cathepsin L (IC₅₀ = 499 and 499.18 nM against human and rabbit enzyme, respectively) and/or cathepsin S, claimed for the treatment of chronic obstructive pulmonary disease. A representative compound from a series of acetamido acetonitrile derivatives.

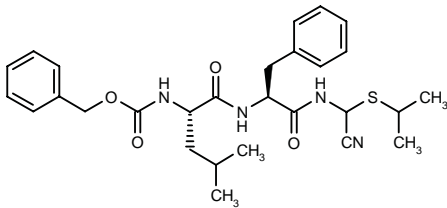
SOURCE – AstraZeneca.

REFERENCES

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293819

N-(Benzyloxycarbonyl)-L-leucyl-L-phenylalanine 1-cyano-1-(isopropylsulfanyl)methylamide



C28 H36 N4 O4 S; Mol wt: 524.6824

ACTION – An inhibitor of cysteine proteases, particularly cathepsin L (IC₅₀ = 38 and 38.27 nM against human and rabbit enzyme, respectively) and/or cathepsin S, claimed for the treatment of chronic obstructive pulmonary disease. A representative compound from a series of di- and tripeptide nitrile derivatives.

SOURCE – AstraZeneca.

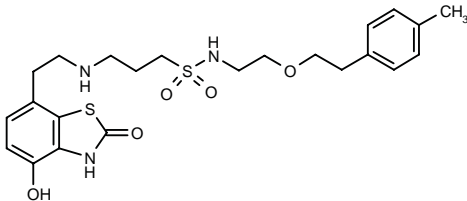
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AR-C89855AA *,3-5

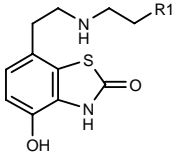
250620

3-[2-(4-Hydroxy-2-oxo-2,3-dihydrobenzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]-propanesulfonamide



C23 H31 N3 O5 S2; Mol wt: 493.6490

ACTION – Dual dopamine D2 receptor and β_2 -adrenoceptor agonist, an analogue of Viozan™ (AR-C68397AA) with improved potency *in vitro* at D2 receptors. In anesthetized dogs, compound exhibited strong and long-lasting β_2 -adrenoceptor- and D2 receptor-agonist properties. When given as an aerosol to β -blocked dogs, it inhibited ammonia-induced reflex mucus production, an effect reversed by the dopamine receptor antagonist domperidone. Moreover, compound inhibited capsaicin-induced neurogenic inflammation in the trachea of anesthetized β -blocked rats. It is in clinical development for the treatment of airways diseases including asthma and chronic obstructive pulmonary disease (COPD). Within this series of chemically related analogues of Viozan™, the following are also described:



Compound	R1	Formula
AR-C68164AA [211498]**,2,4,5	O(CH2)3OCH2CH2Ph	C ₂₂ H ₂₈ N ₂ O ₄ S
AR-C68475AA [250616]***,3-5	NHSO2CH2CH2OCH2CH2Ph	C ₂₁ H ₂₇ N ₃ O ₅ S ₂
AR-C69457AA [254077]***,1,4,5	1-Naph-CH2CH2O-CH2CH2OSO2CH2	C ₂₆ H ₃₀ N ₂ O ₅ S ₂

SOURCE – AstraZeneca.

REFERENCES

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4. Bonnert, R. et al. *The discovery of dual D₂-receptor and β_2 -adrenoceptor agonists for the treatment of airway diseases*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Poster PC161.

5. Young, A. et al. *Novel dual D₂-receptor and β_2 -adrenoceptor agonists for the treatment of airways diseases*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A436.

*Identified compound **250620** (see **250061**) Drug Data Rep 1997, 019(07): 0607.

Identified compound **211498 (see **205560**) Drug Data Rep 1994, 016(09): 0811.

***Identified compound **250616** (see **250061**) Drug Data Rep 1997, 019(07): 0607.

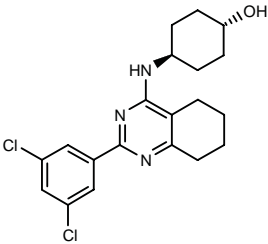
****Identified compound **254077** Drug Data Rep 1997, 019(10): 0887.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

293176

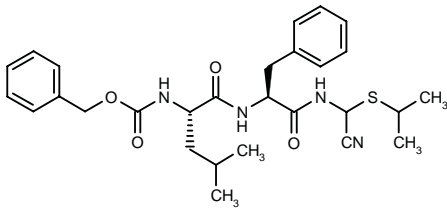
trans-4-[2-(3,5-Dichlorophenyl)-5,6,7,8-tetrahydroquinazolin-4-ylamino]cyclohexanol



C20 H23 Cl2 N3 O; Mol wt: 392.3277

293819

N-(Benzyloxycarbonyl)-L-leucyl-L-phenylalanine 1-cyano-1-(isopropylsulfanyl)methylamide



C28 H36 N4 O4 S; Mol wt: 524.6824

ACTION – An inhibitor of cysteine proteases, particularly cathepsin L (IC₅₀ = 38 and 38.27 nM against human and rabbit enzyme, respectively) and/or cathepsin S, claimed for the treatment of chronic obstructive pulmonary disease. A representative compound from a series of di- and tripeptide nitrile derivatives.

SOURCE – AstraZeneca.

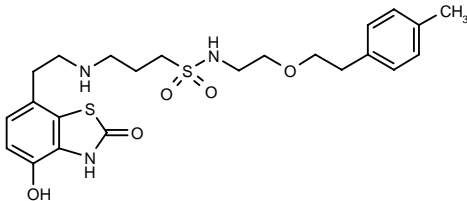
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AR-C89855AA*,3-5

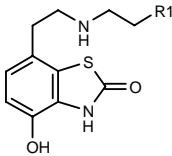
250620

3-[2-(4-Hydroxy-2-oxo-2,3-dihydrobenzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]-propanesulfonamide



C23 H31 N3 O5 S2; Mol wt: 493.6490

ACTION – Dual dopamine D2 receptor and β_2 -adrenoceptor agonist, an analogue of Viozan™ (AR-C68397AA) with improved potency *in vitro* at D2 receptors. In anesthetized dogs, compound exhibited strong and long-lasting β_2 -adrenoceptor- and D2 receptor-agonist properties. When given as an aerosol to β -blocked dogs, it inhibited ammonia-induced reflex mucus production, an effect reversed by the dopamine receptor antagonist domperidone. Moreover, compound inhibited capsaicin-induced neurogenic inflammation in the trachea of anesthetized β -blocked rats. It is in clinical development for the treatment of airways diseases including asthma and chronic obstructive pulmonary disease (COPD). Within this series of chemically related analogues of Viozan™, the following are also described:



Compound	R1	Formula
AR-C68164AA [211498]**,2,4,5	O(CH2)3OCH2CH2Ph	C ₂₂ H ₂₈ N ₂ O ₄ S
AR-C68475AA [250616]***,3-5	NHSO2CH2CH2OCH2CH2Ph	C ₂₁ H ₂₇ N ₃ O ₅ S ₂
AR-C69457AA [254077]***,1,4,5	1-Naph-CH2CH2O-CH2CH2OSO2CH2	C ₂₆ H ₃₀ N ₂ O ₅ S ₂

SOURCE – AstraZeneca.

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1. Bonnert, R. et al. (AstraZeneca plc) *Biologically active benzothiazolone ethanamines*. EP 0918760, JP 2000502681, US 5929100, WO 9723470.

2. Bonnert, R.V. et al. (AstraZeneca AB) *7-(2-Aminoethyl)-benzothiazolones*. EP 0649418, JP 1996503923, US 5648370, WO 9324473.

3. Bonnert, R.V. et al. (AstraZeneca plc) *Benzothiazolone derivs*. JP 1999512422, US 5846989, WO 9710227.

4. Bonnert, R. et al. *The discovery of dual D₂-receptor and β_2 -adrenoceptor agonists for the treatment of airway diseases*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Poster PC161.

5. Young, A. et al. *Novel dual D₂-receptor and β_2 -adrenoceptor agonists for the treatment of airways diseases*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A436.

*Identified compound **250620** (see **250061**) Drug Data Rep 1997, 019(07): 0607.

Identified compound **211498 (see **205560**) Drug Data Rep 1994, 016(09): 0811.

***Identified compound **250616** (see **250061**) Drug Data Rep 1997, 019(07): 0607.

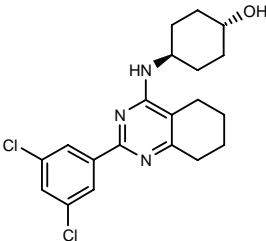
****Identified compound **254077** Drug Data Rep 1997, 019(10): 0887.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

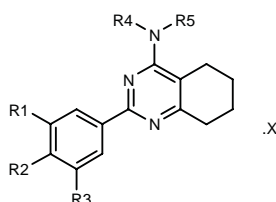
293176

trans-4-[2-(3,5-Dichlorophenyl)-5,6,7,8-tetrahydroquinazolin-4-ylamino]cyclohexanol



C20 H23 Cl2 N3 O; Mol wt: 392.3277

ACTION – Potent guanylate cyclase activator with potential in the treatment and prophylaxis of disorders associated with low cGMP levels including cardiovascular disorders such as hypertension, myocardial infarction, angina pectoris, cardiac insufficiency, thrombosis, pulmonary hypertension, atherosclerosis and stroke, as well as erectile dysfunction, bronchial asthma, chronic renal insufficiency and diabetes. Compound was shown to produce 36-fold stimulation of soluble guanylate cyclase from bovine lung at a concentration of 50 μ M. A representative compound from a series of substituted 4-amino-2-aryltetrahydroquinazolines, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	X	Formula
293177	H	Cl	H	trans-4-OH-cyclohexyl	H	MeSO ₃ H	C ₂₀ H ₂₄ ClN ₃ O .CH ₄ O ₃ S
293178	H	Cl	H	(CH ₂) ₄ OH	H		C ₁₈ H ₂₂ ClN ₃ O
293179	H	Cl	H	trans-4-NH ₂ -cyclohexyl	H		C ₂₀ H ₂₅ ClN ₄
293180	H	Me	H	cyclopentyl	H		C ₂₀ H ₂₅ N ₃
293181	Cl	H	H	trans-4-OH-cyclohexyl	H		C ₂₀ H ₂₄ ClN ₃ O
293182	Cl	H	Cl	trans-4-OH-cyclohexyl	Me		C ₂₁ H ₂₅ Cl ₂ N ₃ O

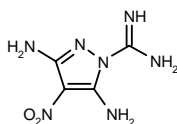
SOURCE – Aventis Pharma.

REFERENCES

1. Schindler, U. et al. (Aventis Pharma Deutschland GmbH) *Subst. 4-amino-2-aryltetrahydroquinazolines, their preparation, their use and pharmaceutical compsns.comprising them*. DE 19904710, WO 0046214.

293781

3,5-Diamino-4-nitro-1*H*-pyrazole-1-carboxamide



C₄ H₇ N₇ O₂; Mol wt: 185.1463

ACTION – Nitric oxide (NO) donor proven to time-dependently release NO in GMK cells at 250 μ M, with a pattern similar to that of the known NO donor SNAP. *In vivo*, compound at a dose of 20 mg/kg exhibited strong blood pressure-lowering activity in spontaneously hypertensive rats.

SOURCES – Friedrich-Schiller-Universität Jena, Jena (DE); NIOPIK, Moscow (RU).

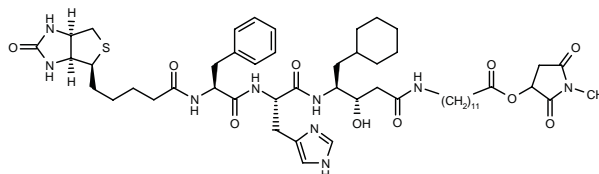
REFERENCES

1. Makarov, V. et al. *4-Nitropyrazole derivatives as new exogenic donors of nitric oxide*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-120.

YS-004-39

293302

(16*S*,17*S*,20*S*,23*S*)-23-Benzyl-17-(cyclohexylmethyl)-16-hydroxy-20-(1*H*-imidazol-4-ylmethyl)-14,19,22,25-tetraoxo-29-[(3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]-13,18,21,24-tetraazanona-cosanoic acid 1-methyl-2,5-dioxopyrrolidin-3-yl ester



C₅₃ H₇₉ N₉ O₁₀ S; Mol wt: 1034.3260

ACTION – A representative compound from a series of reactive derivatives of a known renin inhibitor, which can react with available reactive functionalities on blood components, particularly thiol groups, *in vivo* to form covalent linkages, resulting in conjugated compounds with renin-inhibitory activity and which exhibit extended lifetimes in the bloodstream as compared to the unconjugated parent renin inhibitor, thus providing renin inhibition *in vivo* for longer periods of time. In tests using rabbit erythrocytes, compound was shown to exhibit an extended lifetime of about 200-fold that of the unconjugated compound.

SOURCE – ConjuChem.

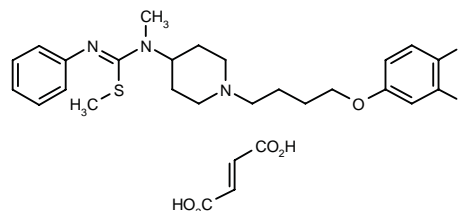
REFERENCES

1. Krantz, A. et al. (ConjuChem, Inc.) *Extended lifetimes in vivo renin inhibitors*. US 6107489.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

292776

*N*¹-[1-[4-(3,4-Difluorophenoxy)butyl]piperidin-4-yl]-*N*¹,*S*-dimethyl-*N*³-phenylisothiourea fumarate



C₂₄ H₃₁ F₂ N₃ O S . C₄ H₄ O₄; Mol wt: 563.6625

ACTION – Cardioprotective and antiischemic agent, as demonstrated *in vitro* by 28% inhibition of veratrine-induced rat left atria contractions at 0.1 μM, as well as by 69% inhibition of ischemic damage in isolated guinea pig hearts subjected to ischemia–reperfusion at 1 μM. Compound was also active in an ischemia–reperfusion model in anesthetized rabbits, in which it reduced the number of arrhythmias and inhibited S-T segment elevation by 58% at a dose of 0.63 mg/kg p.o., without producing a notable effect on heart rate or arterial pressure. Claimed for the treatment of myocardial and cerebral ischemia, stroke, unstable and stable angina, restenosis, neurodegenerative disorders, atherosclerosis, hypertension, heart failure, epilepsy, migraine and pain. A representative compound from a series of substituted 1-(piperidin-4-yl)-3-(aryl)isothioureas.

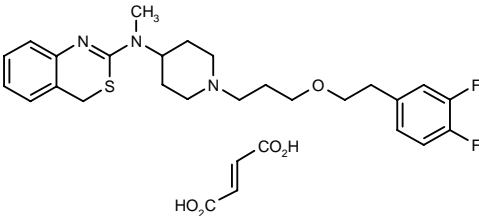
SOURCE – Pierre Fabre.

REFERENCES

1. Patoiseau, J.-F. et al. (Pierre Fabre Médicament) *Substd. 1-(piperidin-4-yl)-3-(aryl)-isothioureas, their preparation and therapeutic use.* FR 2788771, WO 0043011.

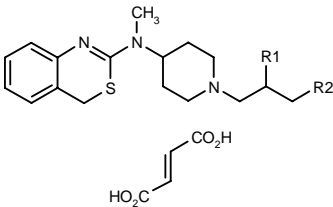
292881

N-(4*H*-3,1-Benzothiazin-2-yl)-*N*-[1-[3-[2-(3,4-difluorophenyl)ethoxy]propyl]piperidin-4-yl]-*N*-methylamine fumarate



C25 H31 F2 N3 O S . C4 H4 O4; Mol wt: 575.6735

ACTION – Cardioprotective and antiischemic agent, as demonstrated *in vitro* by 32% inhibition of veratrine-induced rat left atria contractions at 0.1 μM, as well as by 77% inhibition of ischemic damage in isolated guinea pig hearts subjected to ischemia–reperfusion at 1 μM. Compound was also active in an ischemia–reperfusion model in anesthetized rabbits, in which it completely suppressed reperfusion arrhythmias and inhibited S-T segment elevation by 83% at a dose of 0.63 mg/kg p.o., with a negligible effect on heart rate and arterial pressure. Claimed for the treatment of myocardial and cerebral ischemia, stroke, unstable and stable angina, restenosis, neurodegenerative disorders, atherosclerosis, hypertension, heart failure, epilepsy, migraine and pain. Other compounds from this series of substituted 1-(piperidin-4-yl)-3-(aryl)isothioureas include the following:



Compound	R1	R2	Formula
292882	H	4-F-Ph-CH2CH2OCH2	C26H34FN3OS.C4H4O4
292883	H	4-F-PhCH2CH2O	C25H32FN3OS.C4H4O4
292884	OH	4-F-PhCH2O	C24H30FN3O2S.C4H4O4

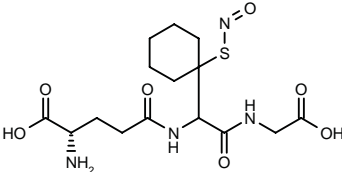
SOURCE – Pierre Fabre.

REFERENCES

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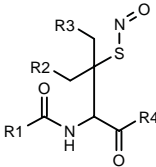
293010

*N*⁵-[2-(Carboxymethylamino)-1-[1-(nitrososulfanyl)cyclohexyl]-2-oxoethyl]-L-glutamine



C15 H24 N4 O7 S; Mol wt: 404.4416

ACTION – Vasodilator and platelet aggregation inhibitor with potential for the treatment of circulatory system disorders, especially cardiovascular disorders. Vaso-dilating activity was demonstrated *in vitro* by relaxation of norepinephrine-contracted arterial rings. In addition, it was shown to inhibit human platelet aggregation (IC₅₀ = 0.047 ± 0.011 μM), being more potent than *S*-nitrosoglutathione (IC₅₀ = 0.48 ± 0.19 μM). Other specifically claimed compounds from this series of *S*-nitrosothiols derived from penicillamine or glutathione are:



Compound	R1	R2	R3	R4	Formula
293012	Me	-CH2OCH2-		OH	C9H14N2O5S
293013	Me	-CH2N(Me)CH2-		OH	C10H17N3O4S
293014	Me	Ph	Ph	OH	C19H20N2O4S
293017	(S)-CH2CH2-CH(NH2)CO2H	-CH2OCH2-		NHCH2CO2H	C14H22N4O6S
293018	(S)-CH2CH2-CH(NH2)CO2H	Ph	Ph	NHCH2CO2H	C24H28N4O7S

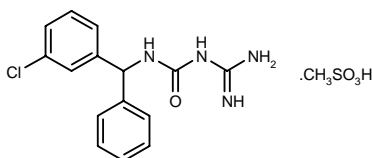
SOURCE – Lacer.

REFERENCES

1. Repolles Moliner, J. et al. (Lacer SA) *S-Nitrosothiols as agents for the treatment of circulatory dysfunctions*. WO 0044714.

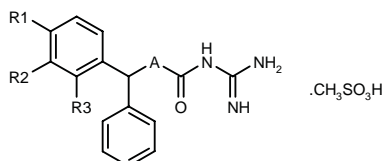
293129

*N*¹-Amidino-*N*³-[1-(3-chlorophenyl)-1-phenylmethyl]jurea methanesulfonate



C₁₅ H₁₅ Cl N₄ O . C H₄ O₃ S; Mol wt: 398.8691

ACTION – An inhibitor of Na⁺/H⁺ exchange (IC₅₀ = 0.14 μM in rat ventricular muscle) with potential in the treatment of cardiovascular, cerebrovascular, renal and proliferative diseases. A representative compound from a series of substituted guanidine derivatives, wherein the following are also included:



Compound	R1	R2	R3	A	Formula
293135	H	Cl	H	O	C ₁₅ H ₁₄ ClN ₃ O ₂ .CH ₄ O ₃ S
293137	Cl	H	H	O	C ₁₅ H ₁₄ ClN ₃ O ₂ .CH ₄ O ₃ S
293138	H	H	H	CH ₂	C ₁₆ H ₁₇ N ₃ O.CH ₄ O ₃ S
293139	H	H	H	O	C ₁₅ H ₁₅ N ₃ O ₂ .CH ₄ O ₃ S
293141	H	H	H	NH	C ₁₅ H ₁₆ N ₄ O.CH ₄ O ₃ S
293143	H	H	Cl	O	C ₁₅ H ₁₄ ClN ₃ O ₂ .CH ₄ O ₃ S
293145	Cl	H	H	NH	C ₁₅ H ₁₅ ClN ₄ O.CH ₄ O ₃ S
293146	H	H	H	-CH ₂ NH-	C ₁₆ H ₁₈ N ₄ O.CH ₄ O ₃ S
293148	H	H	Cl	NH	C ₁₅ H ₁₅ ClN ₄ O.CH ₄ O ₃ S

SOURCE – Sumitomo Pharmaceuticals.

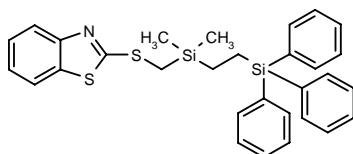
REFERENCES

1. Kitano, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel subst. guanidine derivs. and process for the preparation thereof*. WO 0044707.

OSI-8455

293731

2-[Dimethyl[2-(triphenylsilyl)ethyl]silylmethylsulfanyl]-benzothiazole



C₃₀ H₃₁ N S₂ Si₂; Mol wt: 525.8859

ACTION – Cholesterol-lowering agent, an organosilicon heteroaromatic sulfide proven to reduce total serum cholesterol levels by 31.6% and serum LDL cholesterol from 48.56 mg/dl to 11.27 mg/dl when given to rats at a dose of 10 mg/kg/day for 10 days, while not affecting HDL cholesterol. Potentially useful for the treatment of atherosclerosis.

SOURCE – Latvian Institute of Organic Synthesis, Riga (LV).

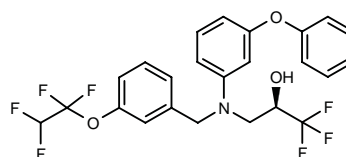
REFERENCES

1. Veveris, M. et al. *Synthesis of organosilicon heteroaromatic sulfides as cholesterol level lowering agents*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-146.

SC-795¹⁻⁵

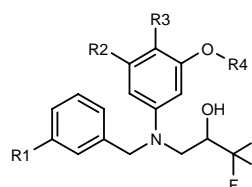
290748

(+)-1,1,1-Trifluoro-3-[*N*-(3-phenoxyphenyl)-*N*-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino]propan-2(*R*)-ol



C₂₄ H₂₀ F₇ N O₃; Mol wt: 503.4120

ACTION – Potent cholesteryl ester transfer protein (CETP) inhibitor (IC₅₀ = 0.02 and 0.6 μM, respectively, in buffer and human plasma), the active (+)-enantiomer of **SC-744**. Potentially useful for increasing plasma HDL cholesterol and lowering the LDL/HDL cholesterol ratio to reduce the risk of atherosclerosis and coronary heart disease. Other related compounds are:



Compound	R1	R2	R3	R4	Isomer	Formula
SC-744 [290749] ¹⁻⁵	OC(F) ₂ CH(F) ₂	H	H	Ph		C ₂₄ H ₂₀ F ₇ NO ₃
SC-554 [293483] ^{1,2,5}	SCF ₃	OMe	OMe	Me	R	C ₂₀ H ₂₁ F ₈ NO ₄ S

SOURCE – Pharmacia.

REFERENCES

1. Sikorski, J.A. et al. (Pharmacia Corp.) *(R)-Chiral halogenated 1-substd.amino-(n+1)-alkanols useful for inhibiting cholesteryl ester transfer protein activity*. WO 0018721, WO 0018724.

2. Durlay, R.C. et al. *Discovery of chiral N,N-disubstituted trifluoro-3-amino-2-propanols as potent inhibitors of cholesteryl ester transfer protein*. J Med Chem 2000, 43(24): 4575.

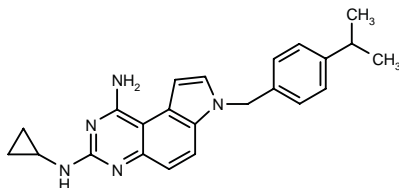
3. Massa, M.A. et al. *Chiral amino alcohols as potent inhibitors of cholesteryl ester transfer protein (CETP)*. 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst A-01.

4. Sikorski, J.A. et al. *New chiral 3-amino-2-propanols as simple, potent inhibitors of cholesteryl ester transfer protein*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-145.

5. Wang, L.J. et al. *New simple class of potent cholesteryl ester transfer protein inhibitors*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 283.

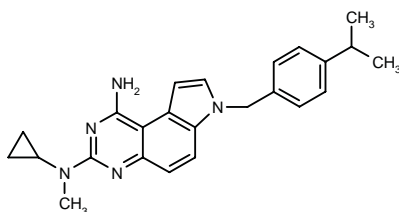
SCH-79797***278879**

*N*³-Cyclopropyl-7-(4-isopropylbenzyl)-7*H*-pyrrolo[3,2-*f*]-quinazoline-1,3-diamine



C₂₃ H₂₅ N₅; Mol wt: 371.4855

ACTION – Nonpeptide thrombin receptor antagonist able to competitively inhibit binding of [³H]-haTRAP to protease-activated receptor-1 (PAR-1) on human platelets (*K*_i = 35 nM). Compound was seen to inhibit aggregation of human platelets induced by α-thrombin and haTRAP (*IC*₅₀ = 300 and 3000 nM, respectively) but not by the tethered ligand agonist for PAR-4, γ-thrombin, ADP or collagen. In human coronary artery smooth muscle cells compound inhibited the transient increase in cytosolic free Ca²⁺ concentrations induced by thrombin and the PAR-1-selective agonist TFLRNPNKD-NH₂ (*K*_i = 82 nM and 55 nM, respectively), while it had no effect on the calcium transients induced by a PAR-2-selective agonist. Moreover, compound was seen to induce potent inhibition of [³H]-thymidine incorporation stimulated by thrombin and TFLRNPNKD-NH₂ (*K*_i = 88 nM and 32 nM, respectively). Potentially useful for reducing the risk of restenosis following angioplasty. Within this series of pyrroloquinazolines, the following is also described:



Sch-203099 [278881]:** C₂₄ H₂₇ N₅

SOURCE – Schering-Plough.

REFERENCES

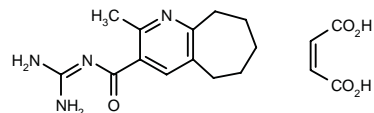
- Ahn, H.-S. et al. *Structure-activity relationships of pyrroloquinazolines as thrombin receptor antagonists*. Bioorg Med Chem Lett 1999, 9(14): 2073.
- Ahn, H.S. et al. *Inhibition of cellular action of thrombin by N³-cyclopropyl-7-[[4-(1-methylethyl)phenyl]methyl]-7*H*-pyrrolo[3,2-*f*]quinazoline-1,3-diamine (SCH 79797), a nonpeptide thrombin receptor antagonist*. Biochem Pharmacol 2000, 60(10): 1425.

*Identified compound **278879** Drug Data Rep 1999, 021(09): 0793.

Identified compound **278881 (see **278879**) Drug Data Rep 1999, 021(09): 0793.

TY-12533**276200**

N'-(2-Methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-ylcarbonyl)guanidine maleate



C₁₃ H₁₈ N₄ O . C₄ H₄ O₄; Mol wt: 362.3838

ACTION – Potent Na⁺/H⁺ exchange inhibitor (*IC*₅₀ = 17 and 32 nM at pH 6.2 and 6.7, respectively) proven to be 4-fold more potent than cariporide at pH 6.7. *In vivo* in an ischemia/reperfusion-induced arrhythmia model in rats, compound given i.v. 5 min before ischemia at doses of 0.01-1 mg/kg significantly reduced the total duration of ventricular tachycardia and it completely abolished ventricular fibrillation and completely prevented mortality at 1 mg/kg; similar results were seen when it was administered 1 min after reperfusion. Compared to cariporide, compound showed almost the same activity when given preocclusion but was more effective when given during ischemia. In addition, a dose of 0.1 mg/kg significantly reduced myocardial infarct size in this model. Potentially useful as adjunctive treatment to coronary interventions such as percutaneous transluminal coronary angioplasty, precutaneous transluminal coronary recanalization and coronary graft surgery.

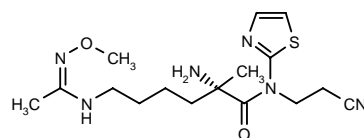
SOURCE – Toa Eiyo.

REFERENCES

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- Aihara, K. et al. *Cardioprotective effect of TY-12533, a novel Na⁺/H⁺ exchange inhibitor, on ischemia/reperfusion injury*. Eur J Pharmacol 2000, 404(1-2): 221.
- Aihara, K. et al. *Protective effects of TY-12533, a novel Na⁺/H⁺ exchanger inhibitor, on myocardial ischemia/reperfusion injury in rats*. Jpn J Pharmacol 1999, 79(Suppl. 1): Abst O-121.

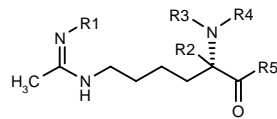
TREATMENT OF SHOCK**293029**

2(*S*)-Amino-*N*-(2-cyanoethyl)-6-[1-(methoxyimino)ethyl-amino]-2-methyl-*N*-(2-thiazolyl)hexanamide

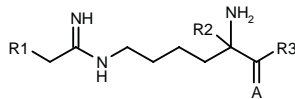


C₁₆ H₂₆ N₆ O₂ S; Mol wt: 366.4874

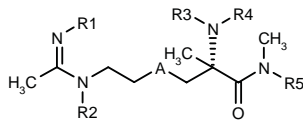
ACTION – Nitric oxide (NO) synthesis modulator that acts by inhibiting the enzyme NO synthase, preferably the inducible isoform. A representative compound from a series of hydroxyamidino carboxylate derivatives, wherein the following are also included:



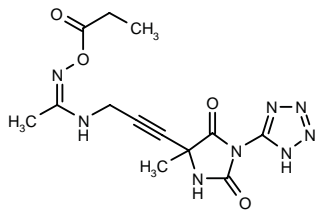
Compound	R1	R2	R3	R4	R5	Formula
293031	t-BuOCO	Me	H	CH2-CH(CN)2	2-imidazolyl-N(Ph)	C ₂₇ H ₃₆ N ₈ O ₃
293032	OH	H	OMe	Ac	2-thiazolyl-NH	C ₁₄ H ₂₃ N ₅ O ₄ S
293041	H	Me	H	H	5-tetrazolyl-N(CH2OAc)	C ₁₃ H ₂₄ N ₈ O ₃



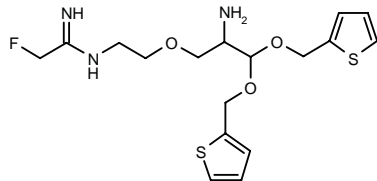
Compound	R1	R2	R3	A	Formula
293043	F	H	2-Piz-CH2S	NH	C ₁₃ H ₂₇ FN ₆ S
293048	H	CH2-CH2OH	2H-tetrazol-5-yl-NHN(Me)	O	C ₁₂ H ₂₅ N ₉ O ₂
293049	H	CH2CN	N(CH2SO2Me)OCH2OMe	O	C ₁₄ H ₂₇ N ₆ O ₅ S



Compound	R1	R2	R3	R4	R5	A	Formula
293036	H	H	cyclopentyl	CO-CH2CF3	2-Pyr	O	C ₂₂ H ₃₂ F ₃ N ₅ O ₃
293039	CH2O-COPh	OH	H	H	5-tetrazolyl	S	C ₁₈ H ₂₆ N ₈ O ₄ S



293038: C₁₃ H₁₆ N₈ O₄



293042: C₁₇ H₂₄ F N₃ O₃ S₂

SOURCE – Pharmacia.

REFERENCES

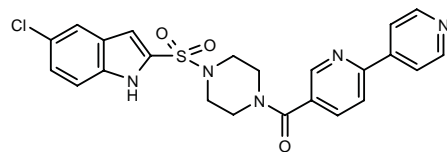
1. Webber, R.K. et al. (Pharmacia Corp.) *Novel hydroxyamidino carboxylate derivs. useful as nitric oxide synthase inhibitors.* WO 0044731.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

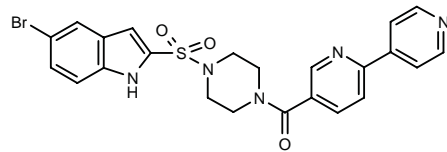
293357

1-[4-(5-Chloro-1*H*-indol-2-ylsulfonyl)piperazin-1-yl]-1-[6-(4-pyridyl)pyridin-3-yl]methanone



C₂₃ H₂₀ Cl N₅ O₃ S; Mol wt: 481.9620

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of human factor Xa. Another exemplified heterocyclic compound is:



293358: C₂₃ H₂₀ Br N₅ O₃ S

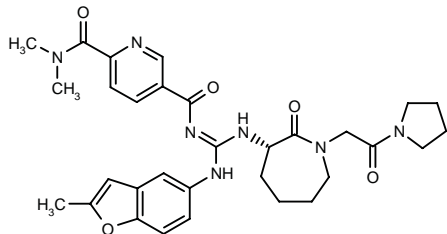
SOURCE – AstraZeneca.

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293516

N,N-Dimethyl-5-[*N*-(*E*)-1-(2-methylbenzofuran-5-yl-amino)-1-[2-oxo-1-[2-oxo-2-(1-pyrrolidiny)ethyl]-hexahydro-1*H*-azepin-3(*S*)-ylamino]methylene]-carbamoyl]pyridine-2-carboxamide



C₃₁ H₃₇ N₇ O₅; Mol wt: 587.6773

ACTION – Anticoagulant, a representative compound from a series of lactam derivatives that inhibit factor Xa. Potentially useful in the treatment of thrombosis, coronary artery disease and cerebrovascular disorders.

SOURCE – Bristol-Myers Squibb.

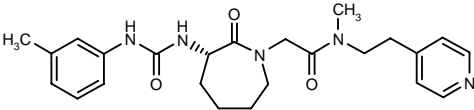
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293521

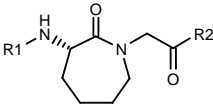
N-Methyl-2-[3(*S*)-[3-(3-methylphenyl)ureido]-2-oxohexahydroazepin-1-yl]-*N*-[2-(4-pyridyl)ethyl]acetamide

N-(3-Methylphenyl)-*N*'-[1-[2-[*N*-methyl-*N*-[2-(4-pyridyl)ethyl]amino]-2-oxoethyl]-2-oxohexahydroazepin-3(*S*)-yl]urea



C24 H31 N5 O3; Mol wt: 437.5409

ACTION – Anticoagulant, a factor Xa inhibitor with potential in the treatment of thromboses, coronary artery disease and cerebrovascular disorders. A representative compound from a series of lactam derivatives, wherein the following are also included:



Compound	R1	R2	Formula
293522	3-Me-PhNHCO	4-PhCH2-1-Piz	C ₂₇ H ₃₆ N ₅ O ₃
293523	2-Naph-SO2	1-pyrrolidinyl	C ₂₂ H ₂₇ N ₃ O ₄ S
293524	3-F-PhNHCO	1-pyrrolidinyl	C ₁₉ H ₂₅ FN ₄ O ₃
293525	CSNHCOPh	1-pyrrolidinyl	C ₂₀ H ₂₆ N ₄ O ₃ S
293526	4-Ac-PhNHCS	1-pyrrolidinyl	C ₂₁ H ₂₆ N ₄ O ₃ S
293527	2-furyl-CONHCS	1-pyrrolidinyl	C ₁₈ H ₂₄ N ₄ O ₄ S
293528	2-Me-5-benzofuryl-NHCS	1-pyrrolidinyl	C ₂₂ H ₂₈ N ₄ O ₃ S

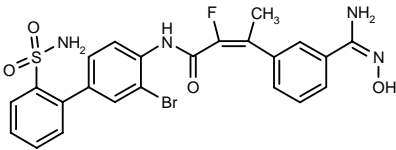
SOURCE – Bristol-Myers Squibb.

REFERENCES

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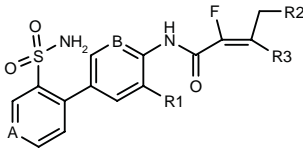
293556

N-(3-Bromo-2'-sulfamoylbiphenyl-4-yl)-2-fluoro-3-[3-(*N*²-hydroxyamidino)phenyl]-2(*E*)-butenamide



C23 H20 Br F N4 O4 S; Mol wt: 547.4030

ACTION – Potent inhibitor of factor Xa with selectivity for factor Xa versus other proteases involved in the coagulation cascade, potentially useful as an antithrombotic agent and as a diagnostic reagent for coagulation disorders. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	A	B	Formula
293557	Br	Me	3-[NH2C(=NH)]-Ph	CH	CH	C ₂₄ H ₂₂ BrFN ₄ O ₃ S
293558	F	H	2-OH-5-[NH2C(=NH)]Ph	CH	CH	C ₂₃ H ₂₀ F ₂ N ₄ O ₄ S
293559	Cl	H	1-NH2-7-isoquinolyl	CH	CH	C ₂₅ H ₂₀ ClFN ₄ O ₃ S
293560	I	H	3-[NH2C(=NOH)]-Ph	CH	CH	C ₂₃ H ₂₀ FIN ₄ O ₄ S
293561	CF3	H	3-[NH2C(=NH)]-Ph	CH	CH	C ₂₄ H ₂₀ F ₄ N ₄ O ₃ S
293562	OH	H	2-OH-5-[NH2C(=NH)]Ph	CH	CH	C ₂₃ H ₂₁ FN ₄ O ₅ S
293563	SH	H	1-NH2-7-isoquinolyl	CH	CH	C ₂₅ H ₂₁ FN ₄ O ₃ S ₂
293564	H	H	3-[NH2C(=NOH)]-Ph	CH	N	C ₂₂ H ₂₀ FN ₅ O ₄ S
293565	OMe	H	3-[NH2C(=NH)]-Ph	CH	CH	C ₂₄ H ₂₃ FN ₄ O ₄ S
293566	Br	H	2-OH-5-[NH2C(=NH)]Ph	N	CH	C ₂₂ H ₁₉ BrFN ₅ O ₄ S

SOURCE – COR Therapeutics.

REFERENCES

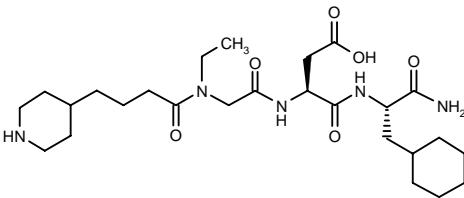
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ANTIPLATELET THERAPY

RGD-891*,1-5

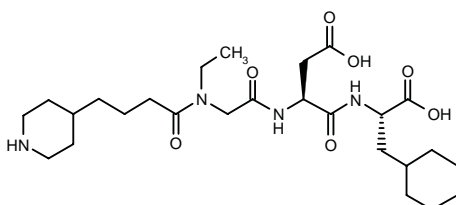
225763

N-Ethyl-*N*-[4-(4-piperidyl)butyryl]-glycyl-L-aspartyl-L-(3-cyclohexyl)alaninamide



C26 H45 N5 O6; Mol wt: 523.6780

ACTION – Water-soluble, low-molecular-weight platelet gpIIb/IIIa receptor antagonist proven to be associated with rapid clearance (11.2-15.5 l/h), limited distribution (23.0-25.9 l) and a short terminal half-life of about 1-2 h in a phase I study in healthy volunteers when administered at doses of 5, 20, 60, 90 and 120 µg/kg as a 4-h i.v. infusion. Rapid and dose-dependent inhibition of ADP-induced platelet aggregation was seen, with > 90% inhibition after a regimen of 60 µg/kg bolus + 336 µg/kg 8-h infusion; platelet aggregation returned to baseline levels at 16-20 h after the end of infusion. Compound was safe and well tolerated at all doses examined, with no clinically relevant abnormalities in vital signs and laboratory parameters. Its active metabolite **RGD-039** showed a longer half-life than the parent compound (4.5-6.6 h). Both the metabolite and the parent compound were mainly eliminated in the urine and showed renal clearance values similar to the glomerular filtration rate.



RGD-039 [225758]:1,2,4,5 C26 H44 N4 O7**

SOURCE – Aventis Pharma.

REFERENCES

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*Identified compound **225763** (see **224160**) Drug Data Rep 1995, 017(09): 0824.

Identified compound **225758 (see **224160**) Drug Data Rep 1995, 017(09): 0824.

THROMBOLYTICS

TENECTEPLASE

Prop INN; USAN

220659

[103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanine]-plasminogen activator (human tissue-type)

TNK-tPA⁺

ACTION – Thrombolytic agent, a recombinant tissue-type plasminogen activator (t-PA).

INDICATION – For reducing mortality associated with acute myocardial infarction.

PRESENTATION – Vials containing lyophilized powder for single i.v. bolus administration after reconstitution with Sterile Water for Injection, 52.5 mg tenecteplase (delivering 50 mg of drug).

PROPRIETARY NAME – **TNKase** (US).

SOURCES – Genentech; copromoted by COR Therapeutics and Schering-Plough.

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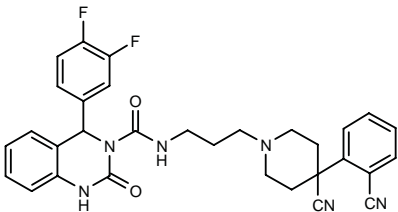
*Drug Data Rep 1995, 017(07): 0642.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

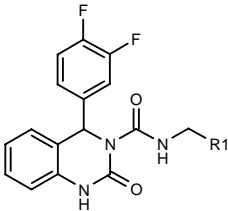
292784

N-[3-[4-Cyano-4-(2-cyanophenyl)piperidin-1-yl]propyl]-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-3-carboxamide



C31 H28 F2 N6 O2; Mol wt: 554.5982

ACTION – α_{1A} -Adrenoceptor antagonist ($K_i < 20$ nM in a binding assay using a transfected human α_{1A} cell line), potentially useful for the treatment of benign prostatic hyperplasia and for increasing urine flow, without hypotensive effects. Other specifically claimed polyazaphthalenone derivatives are:



Compound	R1	Formula
292785	4-(4-F-Ph)-1-Pip-CH2CH2	C ₂₉ H ₂₉ F ₃ N ₄ O ₂
292787	trans-1-[4-(2-CN-Ph)-cyclohexyl]-3-OH-3-azetidiny]	C ₃₂ H ₃₁ F ₂ N ₅ O ₃
292790	trans-1-[4-(2-CN-Ph)-cyclohexyl]-3-azetidiny]	C ₃₂ H ₃₁ F ₂ N ₅ O ₂
292792	trans-1-[4-(2-Pyr)-cyclohexyl]-3-azetidiny]	C ₃₀ H ₃₁ F ₂ N ₅ O ₂

SOURCE – Merck & Co.

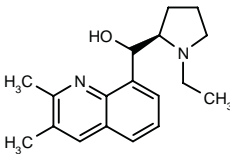
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TREATMENT OF URINARY INCONTINENCE

293166

1-(2,3-Dimethylquinolin-8-yl)-1-[1-ethylpyrrolidin-2(R)-yl]methanol



C18 H24 N2 O; Mol wt: 284.4006

ACTION – Agent with strong urethral contractile activity and weak arterial contractile activity and which also shows venoconstrictive activity, a representative compound from a series of α -azacyclomethyl-quinoline derivatives. Potentially useful for the treatment of urinary incontinence, with reduced cardiovascular side effects compared to conventional agents, as well as for the treatment of venous insufficiency, migraine, gastrointestinal disorders and as a nasal vasoconstrictor.

SOURCE – Sanofi-Synthélabo.

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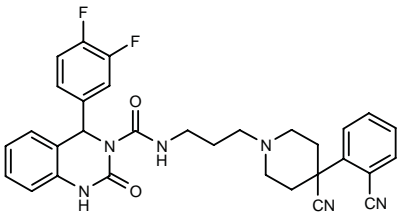
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RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

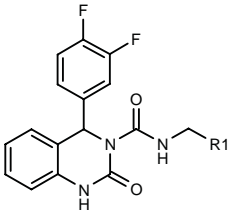
292784

N-[3-[4-Cyano-4-(2-cyanophenyl)piperidin-1-yl]propyl]-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-3-carboxamide



C31 H28 F2 N6 O2; Mol wt: 554.5982

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Compound	R1	Formula
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292787	trans-1-[4-(2-CN-Ph)-cyclohexyl]-3-OH-3-azetidiny]	C ₃₂ H ₃₁ F ₂ N ₅ O ₃
292790	trans-1-[4-(2-CN-Ph)-cyclohexyl]-3-azetidiny]	C ₃₂ H ₃₁ F ₂ N ₅ O ₂
292792	trans-1-[4-(2-Pyr)-cyclohexyl]-3-azetidiny]	C ₃₀ H ₃₁ F ₂ N ₅ O ₂

SOURCE – Merck & Co.

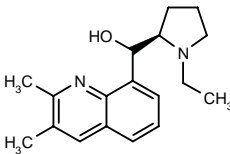
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TREATMENT OF URINARY INCONTINENCE

293166

1-(2,3-Dimethylquinolin-8-yl)-1-[1-ethylpyrrolidin-2(R)-yl]methanol



C18 H24 N2 O; Mol wt: 284.4006

ACTION – Agent with strong urethral contractile activity and weak arterial contractile activity and which also shows venoconstrictive activity, a representative compound from a series of α -azacyclomethyl-quinoline derivatives. Potentially useful for the treatment of urinary incontinence, with reduced cardiovascular side effects compared to conventional agents, as well as for the treatment of venous insufficiency, migraine, gastrointestinal disorders and as a nasal vasoconstrictor.

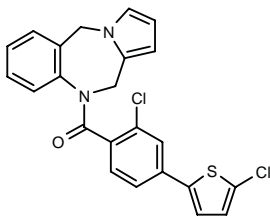
SOURCE – Sanofi-Synthélabo.

REFERENCES

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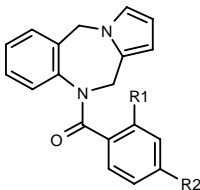
293426

1-[2-Chloro-4-(5-chlorothiien-2-yl)phenyl]-1-(10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-yl)methanone

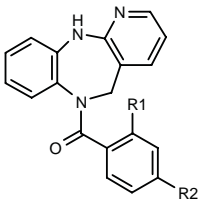


C23 H16 Cl2 N2 O S; Mol wt: 439.3644

ACTION – Selective vasopressin V₂ receptor agonist with no activity at V_{1a} receptors, and thus devoid of hypertensive effects. In water-loaded conscious rats, the compound produced a 74% decrease in urine volume and an 819% increase in urinary osmolality at 10 mg/kg p.o. Potentially useful in the treatment of diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders, and for temporary delay of urination. Other specifically claimed thienylbenzoylbenzazepines are:



Compound	R1	R2	Formula
293427	H	5-Br-2-thienyl	C ₂₃ H ₁₇ BrN ₂ OS
293428	Cl	5-Cl-3-thienyl	C ₂₃ H ₁₆ Cl ₂ N ₂ OS
293429	Cl	2-thienyl	C ₂₃ H ₁₇ ClN ₂ OS
293430	Cl	5-Me-2-thienyl	C ₂₄ H ₁₉ ClN ₂ OS
293431	Cl	3-thienyl	C ₂₃ H ₁₇ ClN ₂ OS



Compound	R1	R2	Formula
293433	Me	2-thienyl	C ₂₄ H ₁₉ N ₃ OS
293434	Cl	5-Cl-2-thienyl	C ₂₃ H ₁₅ Cl ₂ N ₃ OS
293435	Cl	3-thienyl	C ₂₃ H ₁₆ ClN ₃ OS

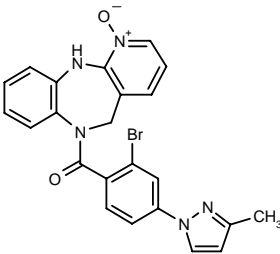
SOURCE – American Home Products.

REFERENCES

1. Failli, A.A. et al. (American Home Products Corp.) *Thienylbenzoylbenzazepines as vasopressin agonists*. WO 0046227.

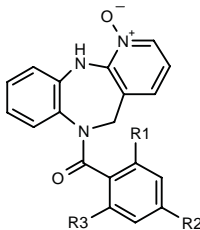
293436

6-[2-Bromo-4-(3-methyl-1*H*-pyrazol-1-yl)benzoyl]-6,11-dihydro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepine 1-oxide



C23 H18 Br N5 O2; Mol wt: 476.3322

ACTION – Selective vasopressin V₂ receptor agonist with no activity at V_{1a} receptors, and thus devoid of hypertensive effects. In water-loaded conscious rats, the compound produced a 90% decrease in urine volume and a 747% increase in urinary osmolality at 10 mg/kg p.o. The compound is useful in the treatment of diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders, and for temporary delay of urination. Other specifically claimed tricyclic pyridine *N*-oxides are:



Compound	R1	R2	R3	Formula
293437	Cl	3-Me-1-pyrazolyl	H	C ₂₃ H ₁₈ ClN ₅ O ₂
293438	CF3	3-Me-1-pyrazolyl	H	C ₂₄ H ₁₈ F ₃ N ₅ O ₂
293439	Cl	5-Me-1-pyrazolyl	H	C ₂₃ H ₁₈ ClN ₅ O ₂
293440	CF3	5-Me-1-pyrazolyl	H	C ₂₄ H ₁₈ F ₃ N ₅ O ₂
293441	CF3	3-CF3-1-pyrazolyl	H	C ₂₄ H ₁₅ F ₆ N ₅ O ₂
293442	F	3-Me-1-pyrazolyl	H	C ₂₃ H ₁₈ FN ₅ O ₂
293443	3-Me-1-pyrazolyl	F	H	C ₂₃ H ₁₈ FN ₅ O ₂
293444	3-Me-1-pyrazolyl	H	Me	C ₂₄ H ₂₁ N ₅ O ₂
293445	CF3	3- <i>t</i> -Bu-1-pyrazolyl	H	C ₂₇ H ₂₄ F ₃ N ₅ O ₂
293446	Cl	1-Me-3-pyrazolyl	H	C ₂₃ H ₁₈ ClN ₅ O ₂
293447	Cl	5-Me-3-pyrazolyl	H	C ₂₃ H ₁₈ ClN ₅ O ₂

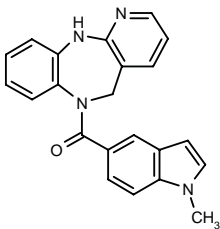
SOURCE – American Home Products.

REFERENCES

1. Failli, A.A. et al. (American Home Products Corp.) *Tricyclic pyridine N-oxides vasopressin agonists*. WO 0046224.

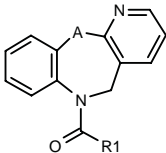
293465

1-(6,11-Dihydro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-6-yl)-1-(1-methyl-1*H*-indol-5-yl)methanone



C22 H18 N4 O; Mol wt: 354.4112

ACTION – Selective vasopressin V₂ receptor agonist with no activity at V_{1a} receptors, and thus devoid of hypertensive effects. In water-loaded conscious rats, the compound produced a 74% decrease in urine volume and a 159% increase in urinary osmolality at 10 mg/kg p.o. Potentially useful in the treatment of diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders, and for temporary delay of urination. A representative compound from a series of pyrido-benzodiazepine and -benzoxazepine carboxyamides, wherein the following are also included:



Compound	R1	A	Formula
293466	1,3-benzodioxol-5-yl	NH	C ₂₀ H ₁₅ N ₃ O ₃
293468	2,3-dihydro-5-benzofuryl	NH	C ₂₁ H ₁₇ N ₃ O ₂
293469	2,1,3-benzoxadiazol-5-yl	NH	C ₁₉ H ₁₃ N ₅ O ₂
293470	6-benzothiazolyl	NH	C ₂₀ H ₁₄ N ₄ OS
293471	1-Me-5-indolyl	O	C ₂₂ H ₁₇ N ₃ O ₂
293472	6-Br-1,3-benzodioxol-5-yl	NH	C ₂₀ H ₁₄ BrN ₃ O ₃

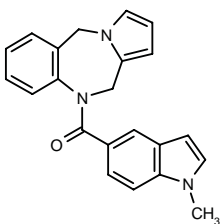
SOURCE – American Home Products.

REFERENCES

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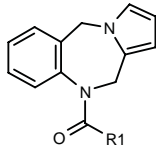
293473

1-(10,11-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-yl)-1-(1-methyl-1*H*-indol-5-yl)methanone



C22 H19 N3 O; Mol wt: 341.4121

ACTION – Selective vasopressin V₂ receptor agonist with no activity at V_{1a} receptors, and thus devoid of hypertensive effects. In water-loaded conscious rats, the compound produced a 66% decrease in urine volume and a 174% increase in urinary osmolality at 10 mg/kg p.o. Potentially useful in the treatment of diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders, and for temporary delay of urination. Other specifically claimed pyrrolobenzodiazepine carboxamides are:



Compound	R1	Formula
293474	1,3-benzodioxol-5-yl	C ₂₀ H ₁₆ N ₂ O ₃
293475	2,3-dihydro-5-benzofuryl	C ₂₁ H ₁₈ N ₂ O ₂
293476	6-benzothiazolyl	C ₂₀ H ₁₅ N ₃ OS
293477	2,1,3-benzoxadiazol-5-yl	C ₁₉ H ₁₄ N ₄ O ₂
293478	6-Br-1,3-benzodioxol-5-yl	C ₂₀ H ₁₅ BrN ₂ O ₃

SOURCE – American Home Products.

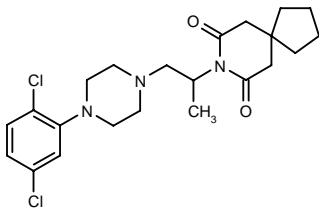
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DV-182

293517

8-[2-[4-(2,5-Dichlorophenyl)piperazin-1-yl]-1-methylethyl]-8-azaspiro[4.5]decane-7,9-dione



C22 H29 Cl2 N3 O2; Mol wt: 438.3961

ACTION – Potent α_{1D} -adrenoceptor antagonist with subnanomolar binding affinity for cloned α_{1D} -adrenoceptors (K_i = 0.41 nM) and high selectivity over α_{1A} - and α_{1B} -adrenoceptors and 5-HT_{1A} receptors (K_i = 186.7, 13.1 and 207 nM, respectively). When compared to the parent compound BMY-7378, compound exhibited similar potency against α_{1D} -adrenoceptors but higher selectivity over 5-HT_{1A} receptors. Potentially useful for the treatment of diseases such as urinary incontinence, vasoconstriction and atherosclerosis.

SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA; Recordati SA, Chemical and Pharmaceutical Company). *Cyclic amides and imides having selective antagonist activity at α -1D adrenergic receptor*. WO 0105765.

2. Barlocco, D. et al. *BMV 7378 analogs as selective antagonists at the α_{1D} adrenergic receptor*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-56.

TREATMENT OF RENAL DISEASES

292840

H-Ala-Gln-Pro-Tyr-Pro-Gln-Gly-Asn-His-Glu-Ala-Ser-Tyr-Gly-OH

C66 H91 N19 O23; Mol wt: 1518.5550

ACTION – Growth-promoting peptide derived from the wound growth factor (WGF) protein that stimulates mitogenic activity of epithelial but not fibroblast cells, particularly kidney epithelial cells, and is thus useful for the treatment of acute renal failure. It was found to increase survival and recovery of renal function in mercuric chloride-induced acute tubular necrosis in rats.

SOURCE – ARCH Development Corp.

REFERENCES

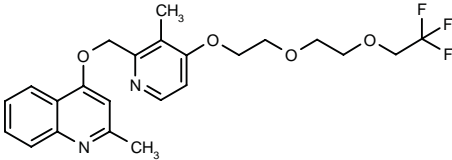
1. Toback, F.G. and Walsh-Reitz, M.M. (ARCH Development Corporation) *Growth-promoting proteins and peptides for kidney epithelial cells*. EP 1034187, US 6096706, WO 9926974.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

293872

2-Methyl-4-[3-methyl-4-[2-[2-(2,2,2-trifluoroethoxy)-ethoxy]ethoxy]pyridin-2-ylmethoxy]quinoline



C23 H25 F3 N2 O4; Mol wt: 450.4545

ACTION – Antiulcer agent active *in vitro* against *Helicobacter pylori* (MIC = 0.012 μ g/ml). A representative compound from a series of quinoline derivatives.

SOURCE – Welfide.

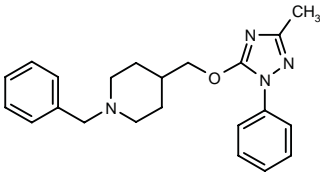
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AGENTS FOR IRRITABLE BOWEL SYNDROME

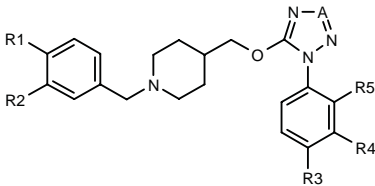
293183

1-Benzyl-4-(3-methyl-1-phenyl-1*H*-1,2,4-triazol-5-yloxy-methyl)piperidine



C22 H26 N4 O; Mol wt: 362.4744

ACTION – Agent for the treatment of irritable bowel syndrome, memory disorders, respiratory disorders and urinary incontinence, a muscarinic M₃ and 5-HT₄ receptor antagonist. Other specifically claimed compounds from this series of triazole and tetrazole derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
293184	H	H	H	H	H	N	C ₂₀ H ₂₃ N ₅ O
293185	H	OH	H	H	H	N	C ₂₀ H ₂₃ N ₅ O ₂
293186	H	H	H	OH	H	-C(Me)-	C ₂₂ H ₂₆ N ₄ O ₂
293187	H	H	Me	H	H	N	C ₂₁ H ₂₅ N ₅ O
293188	H	H	F	H	H	N	C ₂₀ H ₂₂ FN ₅ O
293189	H	OMe	H	H	F	-C(Me)-	C ₂₃ H ₂₇ FN ₄ O ₂
293190	H	OH	H	H	F	-C(Me)-	C ₂₂ H ₂₅ FN ₄ O ₂
293191	SO ₂ NH ₂	H	H	H	H	-C(Me)-	C ₂₂ H ₂₇ N ₅ O ₃ S
293192	H	NH ₂	H	H	H	-C(Me)-	C ₂₂ H ₂₇ N ₅ O

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Bertin, J. et al. (Sanofi-Synthélabo) *Triazole and tetrazole derivs., and their therapeutic use*. FR 2789077, WO 0046220.

SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA; Recordati SA, Chemical and Pharmaceutical Company). *Cyclic amides and imides having selective antagonist activity at α -1D adrenergic receptor*. WO 0105765.

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TREATMENT OF RENAL DISEASES

292840

H-Ala-Gln-Pro-Tyr-Pro-Gln-Gly-Asn-His-Glu-Ala-Ser-Tyr-Gly-OH

C66 H91 N19 O23; Mol wt: 1518.5550

ACTION – Growth-promoting peptide derived from the wound growth factor (WGF) protein that stimulates mitogenic activity of epithelial but not fibroblast cells, particularly kidney epithelial cells, and is thus useful for the treatment of acute renal failure. It was found to increase survival and recovery of renal function in mercuric chloride-induced acute tubular necrosis in rats.

SOURCE – ARCH Development Corp.

REFERENCES

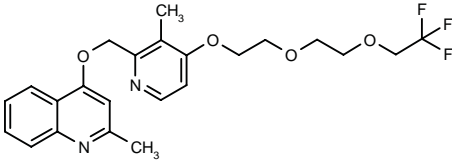
1. Toback, F.G. and Walsh-Reitz, M.M. (ARCH Development Corporation) *Growth-promoting proteins and peptides for kidney epithelial cells*. EP 1034187, US 6096706, WO 9926974.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

293872

2-Methyl-4-[3-methyl-4-[2-[2-(2,2,2-trifluoroethoxy)-ethoxy]ethoxy]pyridin-2-ylmethoxy]quinoline



C23 H25 F3 N2 O4; Mol wt: 450.4545

ACTION – Antiulcer agent active *in vitro* against *Helicobacter pylori* (MIC = 0.012 μ g/ml). A representative compound from a series of quinoline derivatives.

SOURCE – Welfide.

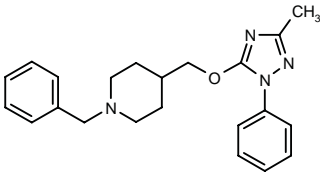
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1. Sano, M. et al. (Welfide Corporation) *Quinoline cpds*. JP 2000212180.

AGENTS FOR IRRITABLE BOWEL SYNDROME

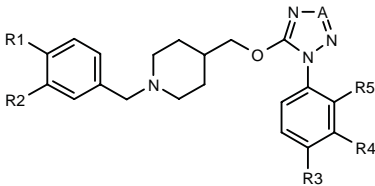
293183

1-Benzyl-4-(3-methyl-1-phenyl-1*H*-1,2,4-triazol-5-yloxy-methyl)piperidine



C22 H26 N4 O; Mol wt: 362.4744

ACTION – Agent for the treatment of irritable bowel syndrome, memory disorders, respiratory disorders and urinary incontinence, a muscarinic M₃ and 5-HT₄ receptor antagonist. Other specifically claimed compounds from this series of triazole and tetrazole derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
293184	H	H	H	H	H	N	C ₂₀ H ₂₃ N ₅ O
293185	H	OH	H	H	H	N	C ₂₀ H ₂₃ N ₅ O ₂
293186	H	H	H	OH	H	-C(Me)-	C ₂₂ H ₂₆ N ₄ O ₂
293187	H	H	Me	H	H	N	C ₂₁ H ₂₅ N ₅ O
293188	H	H	F	H	H	N	C ₂₀ H ₂₂ FN ₅ O
293189	H	OMe	H	H	F	-C(Me)-	C ₂₃ H ₂₇ FN ₄ O ₂
293190	H	OH	H	H	F	-C(Me)-	C ₂₂ H ₂₅ FN ₄ O ₂
293191	SO ₂ NH ₂	H	H	H	H	-C(Me)-	C ₂₂ H ₂₇ N ₅ O ₃ S
293192	H	NH ₂	H	H	H	-C(Me)-	C ₂₂ H ₂₇ N ₅ O

SOURCE – Sanofi-Synthélabo.

REFERENCES

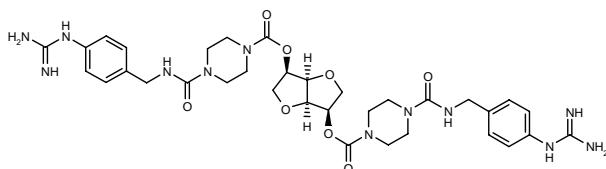
1. Bertin, J. et al. (Sanofi-Synthélabo) *Triazole and tetrazole derivs., and their therapeutic use*. FR 2789077, WO 0046220.

AGENTS FOR INFLAMMATORY BOWEL DISEASE THERAPY

APC-2059

264190

(3*R*,3*aS*,6*R*,6*aS*)-3,6-Bis[4-[*N*-(4-guanidinobenzyl)-carbamoyl]piperazin-1-ylcarbonyloxy]hexahydrofuro-[3,2-*b*]furan



C34 H46 N12 O8; Mol wt: 750.8134

ACTION – Potent human mast cell tryptase inhibitor ($K_i = 0.1$ nM) with high selectivity over other related proteases including trypsin, thrombin and plasmin ($K_i = 15, 138$ and 700 μ M, respectively). *In vivo*, compound exhibited optimal pharmacokinetic and safety profiles and it was effective in blocking the late-phase response and antigen-induced airways hyperresponsiveness in a sheep model of allergic asthma when inhaled at a dose of 500 mg after antigen challenge. Compound is undergoing phase II clinical trials in patients as an injectable therapy for ulcerative colitis and it may also be developed as an inhaled therapy for asthma.

SOURCES – Axys Pharmaceuticals; Bayer.

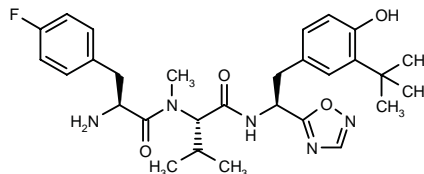
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- AxyS discontinues further development of APC-2059 in psoriasis*. DailyDrugNews.com (Daily Essentials) 1999, Nov 19.
- AxyS continues phase II study of tryptase inhibitor as ulcerative colitis treatment*. DailyDrugNews.com (Daily Essentials) 2000, June 6.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

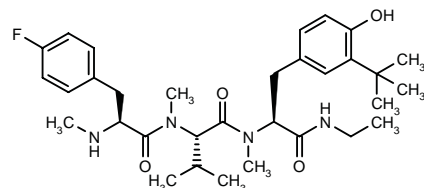
293123

4-Fluoro-L-phenylalanyl-*N* $^{\alpha}$ -methyl-L-valine [2-(3-*tert*-butyl-4-hydroxyphenyl)-1(*S*)-(1,2,4-oxadiazol-5-yl)ethyl]-amide



C29 H38 F N5 O4; Mol wt: 539.6482

ACTION – Potent motilin receptor antagonist, as demonstrated in a binding assay by an IC_{50} value of 0.27 nM for inhibition of [125 I]-motilin binding in rabbit duodenal homogenates and in a functional assay by a pA_2 value of 9.8 for inhibition of acetylcholine-induced contractions of rabbit duodenal longitudinal muscle. Potentially useful for inhibiting gastrointestinal motility. Another compound from this series of phenethylamine derivatives is:



293124: C32 H47 F N4 O4

SOURCE – Chugai.

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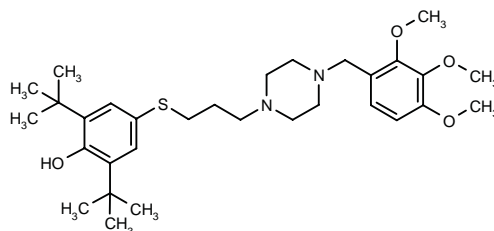
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TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

S-15176

295581

2,6-Di-*tert*-butyl-4-[3-[4-(2,3,4-trimethoxybenzyl)-1-piperazinyl]propylsulfanyl]phenol



C31 H48 N2 O4 S; Mol wt: 544.7962

ACTION – Potent oxygen radical scavenger proven to inhibit lipid peroxidation in liver membranes ($IC_{50} = 0.3 \mu M$) and brain synaptosomes. In rats subjected to 2 h of liver ischemia followed by reperfusion, pretreatment with compound (1.25-10 mg/kg/day i.m. for 5 days before ischemia) was found to increase survival rate and limit tissue damage in a dose-dependent manner, as well as to attenuate the marked increase in serum alanine and aspartate aminotransferase activities seen following ischemia/reperfusion. Compound was also found to reduce elevated plasma oxidized glutathione (GSSG) levels and normalized the elevated plasma GSSG/GSH (reduced glutathione) ratio. Moreover, it significantly attenuated the reduction in glutathione efflux into the bile and partially restored the reduced ATP content in the liver. In addition to these mechanisms, compound was found to inhibit [3H]-trimetazine binding to rat liver mitochondria ($IC_{50} = 0.60$ and $67.8 \mu M$ against site 1 and site 2, respectively). Potentially useful for preventing ischemia/reperfusion injury during liver surgery.

SOURCE – Servier.

REFERENCES

1. Regnier, G. et al. (ADIR et Cie.) *Trimetazidine derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 0533579, FR 2681324, JP 1993194451, US 5283246.

2. Morin, D. et al. [3H]-Trimetazidine mitochondrial binding sites: Regulation by cations, effect of trimetazidine derivatives and other agents and interaction with an endogenous substance. *Br J Pharmacol* 2000, 130(3): 655.

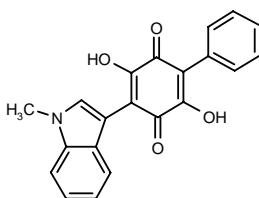
3. Settaf, A. et al. *S-15176 reduces the hepatic injury in rats subjected to experimental ischemia and reperfusion*. *Eur J Pharmacol* 2000, 406(2): 281.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

292659

2,5-Dihydroxy-3-(1-methylindol-3-yl)-6-phenyl-2,5-cyclohexadiene-1,4-dione



C21 H15 N O4; Mol wt: 345.3525

ACTION – Small-molecule activator of the insulin receptor proven to activate insulin receptor tyrosine kinase ($IC_{50} = 300 nM$), while exerting no activity against closely related receptors such as insulin-like growth factor (IGF) receptor, epidermal growth factor (EGF) receptor and platelet-derived growth factor (PDGF) receptor at concentrations up to $30 \mu M$. *In vivo*, a single dose reduced blood glucose levels in hyperglycemic *db/db* mice (0.2-1 mg/kg p.o.) and blood insulin levels in obese *ob/ob* mice (10 mg/kg p.o.). When given once daily for 8-14 days, a significant and dose-dependent reduction in blood glucose levels was seen in hyperglycemic mice (29, 47 and 84% reduction at 0.21, 1 and 10 mg/kg p.o., respectively). No hypoglycemia was observed at up to 10 mg/kg in normal mice and no toxicity at pharmacologically effective doses. Compound exhibited a favorable pharmacokinetic profile, with high oral bioavailability in rats, dogs and monkeys (79, 59 and 66%, respectively). Potentially useful for the treatment of type 2 diabetes.

SOURCE – Merck & Co.

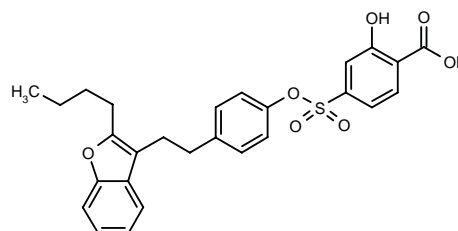
REFERENCES

1. Liu, K. et al. (Merck & Co., Inc.) *Antidiabetic agents*. EP 1067925, US 6077849, WO 9951225.

2. Liu, K. et al. *Discovery of a potent, highly selective, and orally efficacious small-molecule activator of the insulin receptor*. *J Med Chem* 2000, 43(19): 3487.

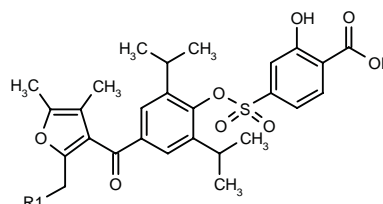
293248

4-[4-[2-(2-Butylbenzofuran-3-yl)ethyl]phenoxy]sulfonyl]-2-hydroxybenzoic acid



C27 H26 O7 S; Mol wt: 494.5614

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor ($IC_{50} = 0.060 \mu M$ against recombinant rat PTP1B), potentially useful for the treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and vascular ischemic diseases. Other exemplified compounds from this series of furan, benzofuran and thiophene derivatives are:



Compound	R1	Formula
293250	Ph	C ₃₃ H ₃₄ O ₆ S
293252	2-Naph	C ₃₇ H ₃₆ O ₆ S
293253	2-Br-Ph	C ₃₃ H ₃₃ BrO ₆ S
293254	4-Br-Ph	C ₃₃ H ₃₃ BrO ₆ S

ACTION – Potent oxygen radical scavenger proven to inhibit lipid peroxidation in liver membranes ($IC_{50} = 0.3 \mu M$) and brain synaptosomes. In rats subjected to 2 h of liver ischemia followed by reperfusion, pretreatment with compound (1.25-10 mg/kg/day i.m. for 5 days before ischemia) was found to increase survival rate and limit tissue damage in a dose-dependent manner, as well as to attenuate the marked increase in serum alanine and aspartate aminotransferase activities seen following ischemia/reperfusion. Compound was also found to reduce elevated plasma oxidized glutathione (GSSG) levels and normalized the elevated plasma GSSG/GSH (reduced glutathione) ratio. Moreover, it significantly attenuated the reduction in glutathione efflux into the bile and partially restored the reduced ATP content in the liver. In addition to these mechanisms, compound was found to inhibit [3H]-trimetazine binding to rat liver mitochondria ($IC_{50} = 0.60$ and $67.8 \mu M$ against site 1 and site 2, respectively). Potentially useful for preventing ischemia/reperfusion injury during liver surgery.

SOURCE – Servier.

REFERENCES

1. Regnier, G. et al. (ADIR et Cie.) *Trimetazidine derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 0533579, FR 2681324, JP 1993194451, US 5283246.

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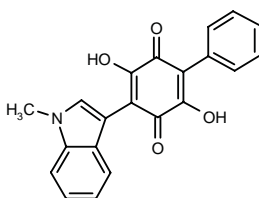
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

292659

2,5-Dihydroxy-3-(1-methylindol-3-yl)-6-phenyl-2,5-cyclohexadiene-1,4-dione



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ACTION – Small-molecule activator of the insulin receptor proven to activate insulin receptor tyrosine kinase ($IC_{50} = 300 nM$), while exerting no activity against closely related receptors such as insulin-like growth factor (IGF) receptor, epidermal growth factor (EGF) receptor and platelet-derived growth factor (PDGF) receptor at concentrations up to $30 \mu M$. *In vivo*, a single dose reduced blood glucose levels in hyperglycemic *db/db* mice (0.2-1 mg/kg p.o.) and blood insulin levels in obese *ob/ob* mice (10 mg/kg p.o.). When given once daily for 8-14 days, a significant and dose-dependent reduction in blood glucose levels was seen in hyperglycemic mice (29, 47 and 84% reduction at 0.21, 1 and 10 mg/kg p.o., respectively). No hypoglycemia was observed at up to 10 mg/kg in normal mice and no toxicity at pharmacologically effective doses. Compound exhibited a favorable pharmacokinetic profile, with high oral bioavailability in rats, dogs and monkeys (79, 59 and 66%, respectively). Potentially useful for the treatment of type 2 diabetes.

SOURCE – Merck & Co.

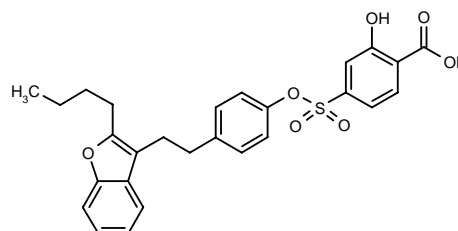
REFERENCES

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2. Liu, K. et al. *Discovery of a potent, highly selective, and orally efficacious small-molecule activator of the insulin receptor*. *J Med Chem* 2000, 43(19): 3487.

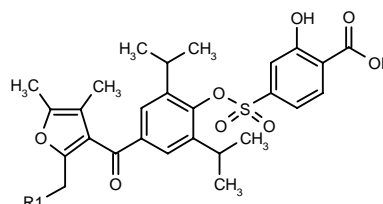
293248

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ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor ($IC_{50} = 0.060 \mu M$ against recombinant rat PTP1B), potentially useful for the treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and vascular ischemic diseases. Other exemplified compounds from this series of furan, benzofuran and thiophene derivatives are:



Compound	R1	Formula
293250	Ph	C ₃₃ H ₃₄ O ₆ S
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293253	2-Br-Ph	C ₃₃ H ₃₃ BrO ₆ S
293254	4-Br-Ph	C ₃₃ H ₃₃ BrO ₆ S

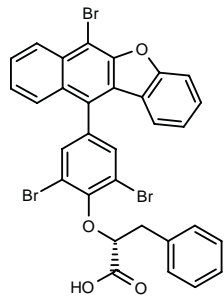
SOURCE – American Home Products.

REFERENCES

1. Dollings, P.J. et al. (American Home Products Corp.) *Furans, benzofurans, and thiophenes useful in the treatment of insulin resistance and hyperglycemia*. US 6103708.

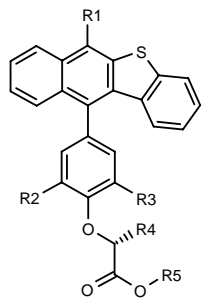
293599

2(R)-[2,6-Dibromo-4-(6-bromonaphtho[2,3-b][1]benzofuran-11-yl)phenoxy]-3-phenylpropionic acid



C31 H19 Br3 O4; Mol wt: 695.1991

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor for the treatment of insulin resistance and hyperglycemia. The compound inhibited rat hepatic microsomal PTPase activity by 60.67% at 50 μM and recombinant rat PTP1B with an IC₅₀ of 0.083 μM. In a standard *in vivo* assay using diabetic *ob/ob* mice, this compound lowered blood glucose levels by 38.7-42.4% at 25 mg/kg by oral gavage. Other exemplified compounds are:



Compound	R1	R2=R3	R4	R5	Formula
293602	Br	i-Pr	H	H	C ₃₀ H ₂₇ BrO ₃ S
293605	Br	Br	Me	H	C ₂₈ H ₁₅ Br ₃ O ₃ S
293606	Br	Ph	H	H	C ₃₆ H ₂₃ BrO ₃ S
293607	Br	Br	CH2Ph	Na	C ₃₁ H ₁₈ Br ₃ NaO ₃ S
293608	OMe	Br	CH2Ph	H	C ₃₂ H ₂₂ Br ₂ O ₄ S
293609	I	Br	CH2Ph	H	C ₃₁ H ₁₉ Br ₂ IO ₃ S

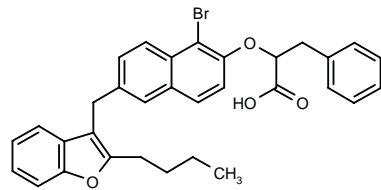
SOURCE – American Home Products.

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1. Wrobel, J.E. et al. (American Home Products Corp.) *11-Aryl-benzo[b]naphtho[2,3-d]-furans and 11-aryl-benzo[b]naphtho[2,3-d]thiophenes useful in the treatment of insulin resistance and hyperglycemia*. US 6110962.

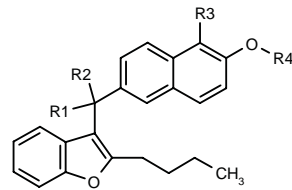
293611

2-[1-Bromo-6-(2-butylbenzofuran-3-ylmethyl)naphthalen-2-yloxy]-3-phenylpropionic acid

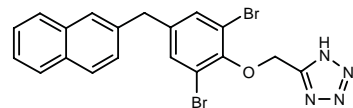


C32 H29 Br O4; Mol wt: 557.4811

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor for the treatment of insulin resistance and hyperglycemia. The compound inhibited rat hepatic microsomal PTPase activity by 59% at 50 μM and recombinant rat PTP1B with an IC₅₀ of 0.37 μM. In a standard *in vivo* assay using diabetic *ob/ob* mice, this compound lowered blood glucose levels by 25.6% at 100 mg/kg by oral gavage. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
293612	H	H	I	CH(CO2H)CH2Ph	C ₃₂ H ₂₉ IO ₄
293613	OH	H	Br	H	C ₂₃ H ₂₁ BrO ₃
293614	-O-		Br	5-tetrazolyl-CH2	C ₂₅ H ₂₁ BrN ₄ O ₃



293615: C19 H14 Br2 N4 O

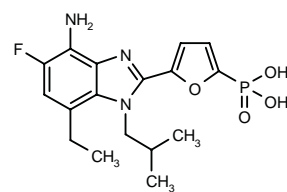
SOURCE – American Home Products.

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1. Malamas, M.S. (American Home Products Corp.) *Aryl-oxo-acetic acids useful in the treatment of insulin resistance and hyperglycemia*. US 6110963.

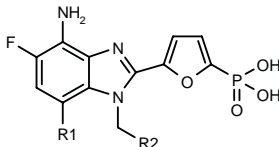
293627

5-(4-Amino-7-ethyl-5-fluoro-1-isobutyl-1H-benzimidazol-2-yl)furyl-2-phosphonic acid



C17 H21 F N3 O4 P; Mol wt: 381.3419

ACTION – Hypoglycemic agent, an inhibitor of fructose-1,6-bisphosphatase (FBPase) at the AMP site. Since this enzyme is required by the gluconeogenesis pathway, the compound may be useful for the treatment of diabetes and diseases related with increased insulin levels. The compound inhibited human, rat and mouse liver FBPases (IC₅₀ = 0.06, 0.55 and 1.07 μM, respectively) and inhibited glucose production in isolated rat hepatocytes (IC₅₀ = 2.5 μM). In studies in rats, the compound lowered blood glucose by 64.6 ± 24% at 20 mg/kg i.p. and by 62 ± 8.6% when administered by oral gavage at 250 mg/kg. Other exemplified benzimidazole derivatives include the following:



Compound	R1	R2	Formula
293628	H	cyclopropyl	C ₁₅ H ₁₅ FN ₃ O ₄ P
293629	(CH2)3Br	i-Pr	C ₁₈ H ₂₂ BrFN ₃ O ₄ P
293630	(CH2)4Br	i-Pr	C ₁₉ H ₂₄ BrFN ₃ O ₄ P
293631	(CH2)3OH	i-Pr	C ₁₈ H ₂₃ FN ₃ O ₅ P
293632	(CH2)3N(Me)2	i-Pr	C ₂₀ H ₂₆ FN ₄ O ₄ P
293633	H	i-Pr	C ₁₅ H ₁₇ FN ₃ O ₄ P

SOURCE – Sankyo.

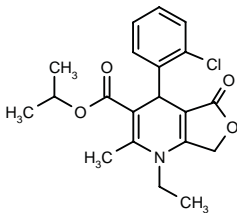
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1. Kasibhatla, S.R. et al. (Sankyo Co., Ltd.) *Benzimidazole inhibitors of fructose 1,6-bisphosphatase*. US 6110903.

BAY-R-3401^{1,3,5}

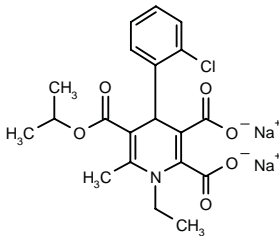
293782

(±)-4-(2-Chlorophenyl)-1-ethyl-2-methyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-*b*]pyridine-3-carboxylic acid isopropyl ester



C20 H22 Cl N O4; Mol wt: 375.8498

ACTION – Orally active hypoglycemic agent, a racemic prodrug which is metabolized by oxidative ring opening to give racemic **Bay-U-6751**, which contains the active enantiomer **Bay-W-1807**, a potent inhibitor of muscle phosphorylase *a* and *b*. In perfused rat liver, the prodrug suppressed hepatic glycogenolysis via inhibition and dephosphorylation of phosphorylase *a*. Potentially useful as an adjuvant in the control of hyperglycemia in type 2 diabetes.



Compound	Isomer	Formula
Bay-U-6751 [141223] ^{*,2,3}	racemic	C ₂₀ H ₂₀ ClNNa ₂ O ₆
Bay-W-1807 [293787] ^{*,4,6}	S	C ₂₀ H ₂₀ ClNNa ₂ O ₆

SOURCE – Bayer.

REFERENCES

1. Goldmann, S. et al. (Bayer AG) *1-Alkyl-substd. 1,4-dihydropyridine lactones, process for their preparation and their use in pharmaceuticals*. DE 3410645, EP 0158138, ES 8607309, ES 8702413, ES 8702414, ES 8702415, ES 8702416, ES 8702417, ES 8702418, ES 8704173, ES 8704174, US 5026714.

2. Goldmann, S. et al. (Bayer AG) *Dihydropyridine derivs*. AU 8777695, DE 3629545, EP 0258729, JP 1988072674.

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*Identified compound **141223** Drug Data Rep 1988, 010(11): 0910.

CLX-0100¹⁻⁵

294903

L-Lysyl-L-threonyl-L-asparaginyl-L-methionyl-L-lysyl-L-histidyl-L-methionyl-L-alanyl-glycyl-L-alanyl-L-alanyl-L-alanyl-L-alanyl-glycyl-L-alanyl-L-valyl-L-valyl-glycine

MC6.1

C70 H121 N23 O21 S2; Mol wt: 1684.9980

ACTION – Orally active antidiabetic agent, an 18-amino-acid peptide isolated from a water-soluble extract of *Momordica charantia* and proven to lower blood glucose levels in streptozotocin-diabetic rats and in NOD mice given oral doses of 2 mg/kg. In a glucose tolerance test in diabetic rats, compound was as effective as recombinant insulin, but unlike insulin, it was not associated with hypoglycemic effects in normal animals. In Zucker rats, a single daily dose of compound strongly reduced serum triglyceride, free fatty acid and cholesterol levels. In addition, the peptide upregulated both GLUT1 and GLUT2 transporters in 3T3-L1 cells without competitive binding activity at insulin receptors. Potentially useful for the treatment of type 1 and late-stage type 2 diabetes. Other related peptides isolated from the same extract are:

H-Lys-Thr-Asn-Met-Lys-His-Met-Ala-Gly-Ala-Ala-OH

CLX-0101 [294904]:^{1,3,4} C47 H82 N16 O14 S2
MC6.2

H-Lys-Thr-Asn-Met-Lys-His-Met-OH

MC6.3 [294905]:^{1,4} C36 H64 N12 O10 S2

SOURCE – Calyx Therapeutics.

REFERENCES

1. Nag, B. et al. (Calyx Therapeutics Inc.) *Orally active fraction of Momordica charantia, active peptides thereof, and their use in the treatment of diabetes.* US 6127338, WO 9843484.

2. Medicherla, S. et al. *Isolation and characterization of a biologically active anti-diabetic peptide from a natural product extract.* FASEB J 2000, 14(8): Abst 221.

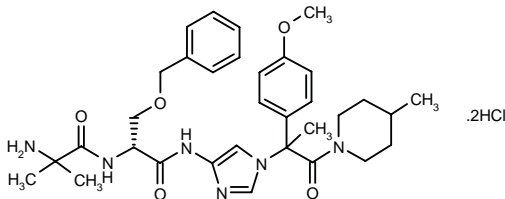
3. Nag, B. et al. *Orally active peptides for the treatment of type I and late-stage type II diabetes.* Diabetes 1999, 48(Suppl. 1): Abst 1552.

4. *Calyx Therapeutics announces issuance of US patent on orally active peptides for treatment of diabetes.* Calyx Therapeutics Press Release 2000, Oct 11.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

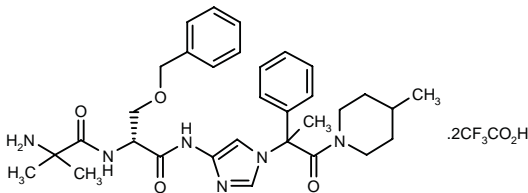
293818

2(R)-(2-Amino-2-methylpropionamido)-3-(benzyloxy)-N-[1-[1-(4-methoxyphenyl)-1-(4-methylpiperidin-1-ylcarbonyl)ethyl]imidazol-4-yl]propionamide dihydrochloride



C33 H44 N6 O5 . 2HCl; Mol wt: 677.6694

ACTION – Growth hormone (GH) secretagogue proven to enhance GH secretion in rat pituitary cell cultures with an EC₅₀ of 2.39 μM. Another exemplified compound from this series of imidazole-containing compounds is:



293820: C32 H42 N6 O4 . 2 C2 H F3 O2

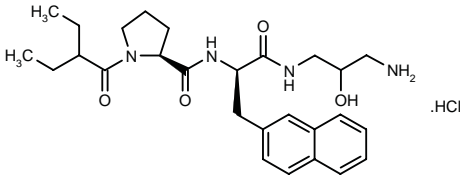
SOURCE – Lilly.

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1. Dodge, J.A. and Lugar, C.W. III (Eli Lilly and Company) *Growth hormone secretagogues.* WO 0049037.

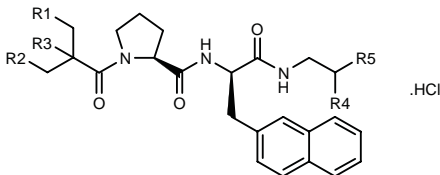
293866

N-(2-Ethylbutyryl)-L-prolyl-3-(2-naphthyl)-D-alanyl (3-amino-2-hydroxypropyl)amide hydrochloride



C27 H38 N4 O4 . HCl; Mol wt: 519.0821

ACTION – Growth hormone (GH) secretagogue whose activity was demonstrated *in vitro* in primary rat anterior pituitary cell preparations at a concentration below 0.01 μM. *In vivo* GH-releasing activity was demonstrated in rats treated with 10 mg/kg p.o. Potentially useful in the treatment or prevention of osteoporosis, catabolic illness, immune deficiency, hip fracture, musculoskeletal impairment in the elderly, GH deficiency in adults or children, obesity, sleep disorders, cachexia and protein loss due to chronic illnesses such as AIDS or cancer, and in the treatment of patients recovering from major surgery, wounds or burns. Other exemplified compounds within this series of amide derivatives include the following:



Compound	R1=R2	R3	R4	R5	Formula
293868	Me	H	NHCOCH2NH2	H	C ₂₈ H ₃₉ N ₅ O ₄ .HCl
293869	H	Me	i-BuNHCH2	OH	C ₃₀ H ₄₄ N ₄ O ₄ .HCl

SOURCES – Kaken; Molecular Research Institute, Mountain View, CA (US).

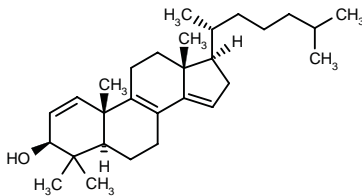
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AGENTS FOR FEMALE INFERTILITY

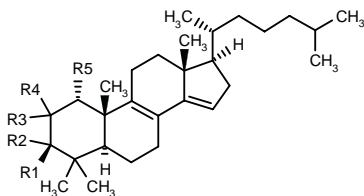
293739

4,4-Dimethyl-5α-cholesta-1,8,14-trien-3β-ol



C29 H46 O; Mol wt: 410.6814

ACTION – Regulator of meiosis in oocytes and in male germ cells, shown to exert meiosis-activating activity in naked mouse oocytes. Other specifically claimed unsaturated cholestane derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
293740	-O-		H	H	CN	C ₃₀ H ₄₅ NO
293741	OH	H	-[4-(C ₇ H ₁₅ CONHCH ₂)-Ph]CH-		H	C ₄₅ H ₆₉ NO ₂

Compounds of the invention that activate meiosis are useful for the treatment of infertility in females and males, and those that inhibit meiosis are useful as contraceptives.

SOURCE – Schering AG.

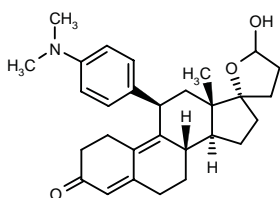
REFERENCES

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CONTRACEPTIVES

293409

(17*R*)-5'-Hydroxy-11β-[4-(dimethylamino)phenyl]spiro[estra-4,9-dien-17,2'-tetrahydrofuran]-3-one



C29 H37 N O3; Mol wt: 447.6153

ACTION – Steroid with antiprogesterogenic and antiglucocorticoid activities, as demonstrated by measuring the relative binding affinity (RBA) to human cloned progesterone and glucocorticoid receptors compared to cloned human estrogen receptors, androgen receptors from rat prostate and mineralocorticoid receptors from rat kidney (RBA = 303, 75, 0, 32 and 40, respectively). In addition, compound was found to be 75% effective as an abortive in rats at 10 mg/kg p.o. Potentially useful as a contraceptive, in the treatment of hormonal disorders including progesterone-dependent tumors, and also for combatting the adverse effects of corticoids. A representative compound from a series of 11β-[4-(*N*-dimethylamino)phenyl]estra-4,9-dien-3-one derivatives with spiro-lactol substitution at position 17.

SOURCE – CNRS.

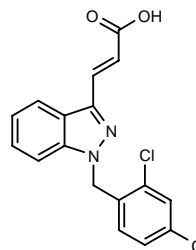
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AF-2785

294795

3-[1-(2,4-Dichlorobenzyl)-1*H*-indazol-3-yl]-2(*E*)-propenoic acid



C17 H12 Cl2 N2 O2; Mol wt: 347.1998

ACTION – A lonidamine analogue that blocks the cAMP-activated chloride channel in epididymal cells (IC₅₀ = 170.6 μM) encoded by the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which plays an important role in male reproduction. Moreover, in cultured rat epididymal epithelia, compound inhibited cAMP-stimulated chloride secretion, measured as short-circuit current, much more potently than known chloride channel blockers. A potential lead compound for the discovery of new male contraceptives.

SOURCE – Angelini.

REFERENCES

1. Silvestrini, B. and Cheng, C.Y. (Angelini Pharmaceuticals Inc.) *3-Substd. 1-benzyl-1*H*-indazole derivs. as antifertility agents*. US 6001865.

2. Gong, X.D. et al. *Lonidamine and analogue AF2785 block the cyclic adenosine 3',5'-monophosphate-activated chloride current and chloride secretion in the rat epididymis*. Biol Reprod 2000, 63(3): 833.

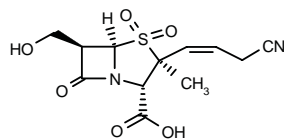
ANTIINFECTIVE THERAPY

ANTIBIOTICS

292851

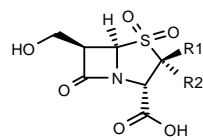
(2*S*,3*S*,5*R*,6*R*)-3-[3-Cyano-1 (*Z*)-propenyl]-6-(hydroxy-methyl)-3-methyl-4,4,7-trioxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid

(2*S*,3*S*,5*R*,6*R*)-2-[3-Cyano-1 (*Z*)-propenyl]-6-(hydroxy-methyl)-2-methylpenam-3-carboxylic acid *S,S*-dioxide



C12 H14 N2 O6 S; Mol wt: 314.3166

ACTION – β -Lactamase inhibitor active against both class A and class C serine β -lactamases, with IC₅₀ values of 19 and 270 nM, respectively, against TEM-1 (class A) and AmpC (class C) β -lactamase enzymes. Synergistic antibacterial activity was demonstrated in *in vitro* assays with a 1:1 combination of this compound and piperacillin against *Escherichia coli* and *Serratia marcescens* (MIC = 4 and 8 μ g/ml vs. > 64 and 32 μ g/ml, respectively, for piperacillin alone). Other specifically claimed 3,6-disubstituted penam sulfone derivatives are:



Compound	R1	R2	Formula
292852	1,2,3-triazolyl-1-yl-CH2	Me	C ₁₁ H ₁₄ N ₄ O ₆ S
292853	Me	CH2NHOMe	C ₁₀ H ₁₆ N ₂ O ₇ S
292854	(E)-CH=CHCH2CN	Me	C ₁₂ H ₁₄ N ₂ O ₆ S

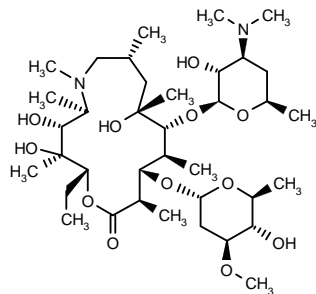
SOURCE – American Home Products.

REFERENCES

1. Lin, Y.-I. et al. (American Cyanamid Co.) *3,6-Disubstd. penam sulfone derivs. as antibacterials*. WO 0043399.

293236

3''-Demethyl-9-deoxo-9a-methyl-9a-azaerythromycin A



C37 H70 N2 O12; Mol wt: 734.9620

ACTION – Macrolide antibiotic with a broad spectrum of activity against bacterial and protozoal organisms, as well as antitumor activity. This compound has the advantage of increased acid stability when compared with other azalides such as azithromycin.

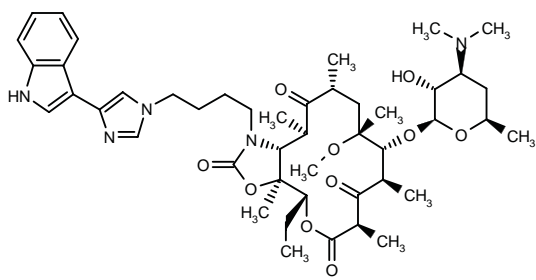
SOURCE – Pfizer.

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1. O'Connell, T.N. et al. (Pfizer Products Inc.) *Novel azalides and methods of making same*. EP 1024145, JP 2000219697.

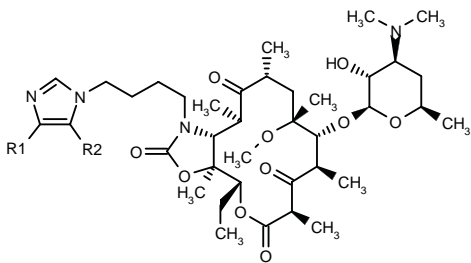
293266

11,12-Dideoxy-3-de(2,6-dideoxy-3-*C*-methyl- α -L-ribohexopyranosyloxy)-6-*O*-methyl-3-oxo-11-[4-[4-(1*H*-indol-3-yl)imidazol-1-yl]butylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C46 H67 N5 O10; Mol wt: 850.0603

ACTION – Antibacterial erythromycin derivative with potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011UC4 (MIC = 0.040 μ g/ml), *Staphylococcus epidermidis* 012GO11i (MIC = 0.080 μ g/ml), *Streptococcus pyogenes* 02A1UC1 (MIC = 0.02 μ g/ml), *Streptococcus agalactiae* 02B1HT1 (MIC = 0.02 μ g/ml), *Enterococcus faecalis* 02D2UC1 (MIC = 0.040 μ g/ml), *Enterococcus faecium* 02D3HT1 (MIC = 0.02 μ g/ml), *Streptococcus mitis* 02MitCB1 (MIC = 0.02 μ g/ml) and *Streptococcus pneumoniae* 032UC1 (MIC = 0.02 μ g/ml). Also reported to be active against *Haemophilus influenzae*, *Rickettsia*, *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella*, *Ureaplasma*, *Toxoplasma* and *Mycobacterium* spp. Other specifically claimed compounds from this series of erythromycin derivatives are:



Compound	R1	R2	Formula
293267	2-furyl-CONH	H	C ₄₃ H ₆₅ N ₅ O ₁₂
293269	-N=C(Cl)CH=CH-		C ₄₁ H ₆₂ ClN ₅ O ₁₀

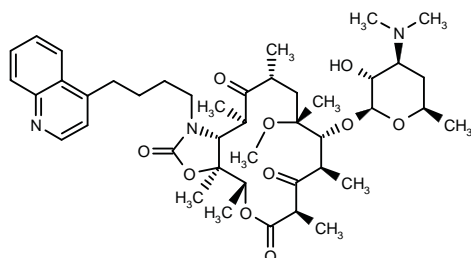
SOURCE – Aventis Pharma.

REFERENCES

1. Denis, A. et al. (Aventis Pharma SA) *Erythromycin derivs., their preparation and use as medicaments*. EP 1026170, FR 2789392, JP 2000229993.

293859

11,12-Dideoxy-13-des(ethyl)-3-des(hexopyranosyloxy)-13-methyl-6-*O*-methyl-3-oxo-11-[4-(4-quinolinyl)-butylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C43 H63 N3 O10; Mol wt: 781.9817

ACTION – Ketolide antibiotic, an analogue of erythromycin with broad-spectrum activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MIC = 0.25 µg/ml), staphylococci with *erm* resistance mechanism (MIC = 0.5 µg/ml), *Streptococcus haemolyticus* with *msr* resistance mechanism (MIC = 0.5 µg/ml), *Streptococcus pneumoniae* (MIC = 0.03 µg/ml) and *S. pneumoniae* with *erm* or *mef* resistance mechanism (MIC = 0.25 and 0.12 µg/ml, respectively). Compound was also effective in a mouse *S. aureus* systemic infection model, affording 80% protection at a dose of 20 mg/kg s.c.

SOURCES – Kosan; R.W. Johnson.

REFERENCES

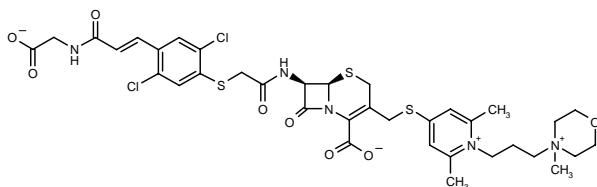
1. Hlasta, D. et al. (Ortho-McNeil Pharmaceutical, Inc.;Kosan Biosciences, Inc.) *Ketolide antibacterials*. WO 0062783.
2. Bush, K. et al. *In vitro and in vivo SAR of ketolides derived from R13-modified erythromycin A and picromycin core structures*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abstr F-1821.

BMS-247243

293393

(6*R*,7*R*)-7-[2-[4-[3-(Carboxylatomethylamino)-3-oxo-1(*E*)-propenyl]-2,5-dichlorophenylsulfanyl]acetamido]-3-[2,6-dimethyl-1-[3-(4-methylmorpholin-4-iumyl)propyl]-pyridinium-4-ylsulfanylmethyl]-3-cephem-4-carboxylate

(6*R*,7*R*)-7-[2-[4-[3-(Carboxylatomethylamino)-3-oxo-1(*E*)-propenyl]-2,5-dichlorophenylsulfanyl]acetamido]-3-[2,6-dimethyl-1-[3-(4-methylmorpholin-4-iumyl)propyl]-4-pyridiniumylsulfanylmethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



C36 H41 Cl2 N5 O8 S3; Mol wt: 838.8509

ACTION – Cephalosporin antibiotic with excellent activity against methicillin-susceptible and methicillin-resistant staphylococci (MIC₉₀ ranging from 0.25 to 4 µg/ml), being 2-fold more active than vancomycin. Compound was also active against streptococci, pneumococci, enterococci and some anaerobic Gram-positive strains, but showed generally little or no activity against Gram-negative bacteria. Compound showed comparable antibacterial activity to cefotaxime against streptococci and pneumococci; MIC₉₀ values against *Streptococcus pneumoniae* susceptible, intermediately resistant and resistant to penicillin were 0.06, 0.12 and 2 µg/ml, respectively, for compound and 0.03, 0.25 and 2 µg/ml, respectively, for cefotaxime. Against *Enterococcus faecalis* compound was more active than cefotaxime (MIC₉₀ = 4 and > 128 µg/ml, respectively). The compound was also found to be more rapidly bactericidal against methicillin-resistant *Staphylococcus aureus* (MRSA) than vancomycin and it was synergistic with streptomycin against streptomycin-susceptible enterococcal strains. Compound was also found to be efficacious in systemic infections in mice induced by *S. aureus* (ID₅₀ = 0.9 mg/kg i.m.), MRSA (ED₅₀ = 2-3.2 mg/kg i.m.), *Streptococcus pyogenes* (ED₅₀ = 0.2 mg/kg i.m) and *Enterococcus faecalis* (ED₅₀ = 6.2-7.6 mg/kg i.m.). In addition, this new cephem was active against localized muscle infections in leukopenic mice caused by MRSA or by *S. pneumoniae*, as well as in an MRSA model of endocarditis in rabbits.

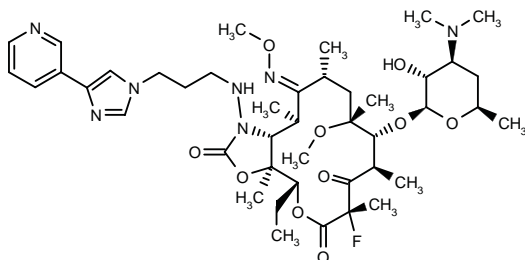
SOURCE – Bristol-Myers Squibb.

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2. Fung-Tomc, J. et al. *Anti-staphylococcal activity of a novel MRSA (methicillin-resistant *Staphylococcus aureus*) cephem BMS-247243*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abstr F-1063.
3. Huczko, E. et al. *Antibacterial spectrum of a novel MRSA (methicillin-resistant *Staphylococcus aureus*) cephem BMS-247243*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abstr F-1064.
4. Kim, O. et al. *Discovery, synthesis and SAR of BMS-247243, a novel cephalosporin active against methicillin-resistant *Staphylococcus aureus* (MRSA) and susceptible *Staphylococcus aureus* (MSSA)*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abstr F-1062.
5. Kolek, B. et al. *Bactericidal activity of the novel anti-MRSA (methicillin-resistant *Staphylococcus aureus*) cephem BMS-247243 to MRSA and enterococci*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abstr F-1065.
6. Lamb, L. et al. *In vivo evaluation of a novel MRSA (methicillin-resistant *Staphylococcus aureus*) cephem, BMS-247243*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abstr F-1066.
7. Singh, J. et al. *A practical synthesis of an anti-methicillin resistant *Staphylococcus aureus* cephalosporin BMS-247243*. Org Process Res Dev 2000, 4(6): 488.

CP-654743**293019**

3-Des(hexopyranosyloxy)-9-deoxy-11-deoxy-2-fluoro-9-(methoxyimino)-6-*O*-methyl-3-oxo-11-[3-[4-(3-pyridyl)-imidazol-1-yl]propylhydrazino]erythromycin A 11-*N*¹,12-*O*-cyclic carbamate



C43 H66 F N7 O10; Mol wt: 860.0314

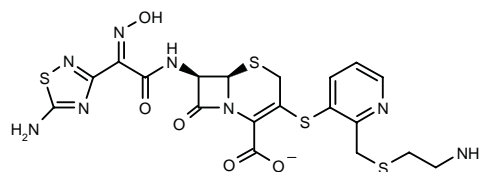
ACTION – Ketolide antibiotic active *in vitro* against macrolide-resistant respiratory pathogens including *Streptococcus pneumoniae*, *S. pneumoniae* with *erm*(B) or *mef*(A) resistance mechanisms, *Haemophilus influenzae* and *Streptococcus pyogenes* with *erm*(B)/*erm*(A) resistance mechanisms (MIC₉₀ = 0.004, 0.125-0.25, 2.0 and 6.3 µg/ml, respectively). In animal infection models, compound exhibited comparable activity to telithromycin in murine peritonitis caused by macrolide-resistant (MLS_B and *mef*(A)) *S. pneumoniae* (ED₅₀ = 23-43 mg/kg p.o. vs. 15-49 mg/kg p.o.), murine pneumonia caused by susceptible (ED₅₀ = 4.5 mg/kg p.o. vs. 3.1 mg/kg p.o.) and macrolide-resistant (MLS_B and *mef*(A)) *S. pneumoniae* (ED₅₀ = 18-28 mg/kg p.o. vs. 23-31 mg/kg p.o.), and gerbil middle ear infection caused by susceptible *H. influenzae* (ED₅₀ = 23 mg/kg p.o. vs. 21 mg/kg p.o.). Compound exhibited a good pharmacokinetic profile, with good distribution properties and a large volume of distribution in rats, dogs and monkeys following i.v. administration. Additionally, Caco-2 permeability studies predicted good intestinal absorption of compound in man.

SOURCE – Pfizer.**REFERENCES**

1. Kaneko, T. and McMillen, W.T. (Pfizer Products Inc.) *Ketolide antibiotics*. WO 0044761.
2. Girard, D. et al. *In vivo antibacterial activity of CP-654,743, a new C2-fluoro ketolide, against macrolide resistant pneumococci and Haemophilus influenzae*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1816.
3. Girard, D. et al. *Pharmacokinetics of CP-654,743, a new C2-fluoro ketolide active against macrolide resistant respiratory pathogens, in preclinical species*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1817.
4. Kaneko, T. et al. *Synthesis and in vitro activity of C2-substituted C9-oxime ketolides*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1815.

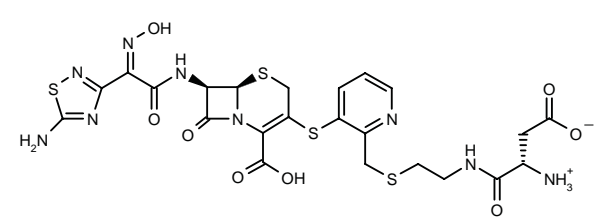
RWJ-333441/MC-04,546¹⁻¹⁰**293401**

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[2-(2-ammonioethyl)sulfanylmethyl]pyridin-3-ylsulfanyl]-3-cephem-4-carboxylate



C19 H20 N8 O5 S4; Mol wt: 568.6820

ACTION – Cephalosporin antibiotic with bactericidal activity against methicillin-resistant staphylococci and other Gram-positive bacteria. Compound exhibited strong activity against methicillin-resistant *Staphylococcus aureus* (MRSA; MIC = 1 µg/ml), which correlated with its enhanced affinity for PBP2a (IC₅₀ = 0.8 µg/ml). It was as effective as vancomycin and more potent than imipenem against MRSA and coagulase-negative staphylococci (MIC₉₀ = 2 µg/ml), and it was more active than ampicillin, vancomycin, ciprofloxacin and gentamicin against ampicillin-sensitive *Enterococcus faecium* (MIC₉₀ = 4 µg/ml) and *Enterococcus faecalis* including strains resistant to vancomycin, ciprofloxacin and gentamicin (MIC₉₀ = 1 µg/ml). Against penicillin-resistant or intermediately resistant strains of *Streptococcus pneumoniae*, it was more active than cefotaxime and ciprofloxacin and almost equieffective to vancomycin, with MIC₉₀ values of 0.25-0.5 µg/ml, and it was as effective as penicillin G and cefotaxime against penicillin-susceptible strains. Compound showed good activity against *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC₉₀ = 2 µg/ml), but showed low activity against other Gram-negative organisms. Excellent *in vivo* efficacy was seen in a murine model of sepsis caused by methicillin-susceptible *S. aureus* (MSSA; ED₅₀ = 0.39 mg/kg s.c.). The L-aspartyl prodrug **RWJ-333442/MC-04,699** was found to have an aqueous solubility of > 20 mg/ml and a relative availability of the active form in rats of 100%. In murine models of sepsis caused by MSSA and MRSA, the prodrug was more potent than vancomycin and Synercid® (quinupristin/dalfopristin), with ED₅₀ values of 0.4 and 1.4 mg/kg s.c., respectively, versus values of 2.7 mg/kg s.c. or greater for vancomycin and Synercid®. It also showed high efficacy in a thigh infection model due to MRSA and a sustained antibacterial effect after a single dose. Pharmacokinetic studies in mice, rats, rabbits and rhesus monkeys demonstrated that the prodrug was rapidly and extensively (> 70%) converted to RWJ-333441 in all species, and the pharmacokinetics of RWJ-333441 (administered as the prodrug) compared favorably with currently available cephalosporin antibiotics.



RWJ-333442 [293405]^{3,6-8,10} C23 H25 N9 O8 S4
MC-04,699

SOURCES – Microcide; R.W. Johnson.

REFERENCES

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2. Blais, J. et al. *RWJ-333441 (MC-04,546), a new cephalosporin with high affinity for PBP 2a and stability to staphylococcal beta-lactamases*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1072.

3. Chen, S.A. et al. *Pharmacokinetics of a novel cephalosporin RWJ-333441 (MC-04,546) and its L-aspartyl prodrug RWJ-333442 (MC-04,699) in mice, rats, rabbits and rhesus macaques*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1077.

4. Foleno, B. et al. *In vitro activity of aztreonam, fosfomycin, gentamicin or levofloxacin against Gram-negative bacteria in the presence of the cephalosporins RWJ-54428 (MC-02,479) or RWJ-333441 (MC-04,546)*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1075.

5. Glinka, T. et al. *Discovery of novel anti-MRSA cephalosporin RWJ-333441 (MC-04,546). Relationships between structure, antibacterial activity, serum stability, pharmacokinetics and efficacy in a series of (3-heteroarylthio)cephems*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1071.

6. Griffith, D. et al. *Efficacy of RWJ-333441 (MC-04,546) when administered as the L-aspartyl prodrug RWJ-333442 (MC-04,699) in the treatment of experimental murine infections due to Staphylococcus aureus*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1078.

7. Griffith, D. et al. *Pharmacodynamics of RWJ-333441 (MC-04,546) when administered as the L-aspartyl prodrug RWJ-333442 (MC-04,699) against Staphylococcus aureus in the neutropenic mouse thigh infection model*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-2248a.

8. Hecker, S.J. et al. *Prodrugs of anti-MRSA cephalosporin RWJ-333441 (MC-04,546) with improved aqueous solubility*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1076.

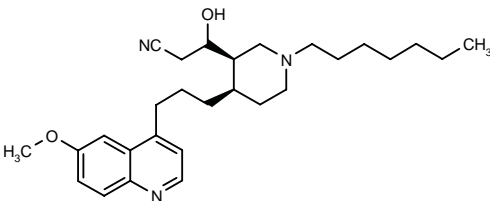
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10. Price, M.E. et al. *Solubility and bioavailability of amino acid prodrugs of a new anti-MRSA cephalosporin RWJ-333441 (MC-04,546)*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2135.

ANTIBACTERIAL DRUGS

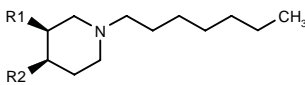
292832

3-[1-Heptyl-4(*R*)-[3-(6-methoxyquinolin-4-yl)propyl]-piperidin-3(*R*)-yl]-3-hydroxypropionitrile



C28 H41 N3 O2; Mol wt: 451.6509

ACTION – Antibacterial piperidinyquinoline with protein tyrosine kinase-inhibitory activity, active against a wide range of organisms including both Gram-negative and Gram-positive bacteria. It exhibited MIC values of 1 µg/ml or less against *Staphylococcus aureus* Oxford, *S. aureus* WCUH29, *S. aureus* Carter 37, *Enterococcus faecalis* I, *Moraxella catarrhalis* Ravasio and *Streptococcus pneumoniae* R6. Other specifically claimed compounds include the following:



Compound	R1	R2	Isomer	Formula
292834	CH2CH2-CO2H	6-MeO-4-quinolyl-(CH2)3	3R,4R	C ₂₈ H ₄₂ N ₂ O ₃
292835	CH(OH)-CH2CO2H	6-MeO-4-quinolyl-(CH2)3	3R,4R	C ₂₈ H ₄₂ N ₂ O ₄
292836	CO2Et	6-MeO-1,5-naphthyridin-4-yl-NHCONH	3RS,4SR	C ₂₅ H ₃₇ N ₅ O ₄
292838	CH2CN	6-MeO-4-quinolyl-CH(OH)CH2CH2	3R,4R	C ₂₇ H ₃₉ N ₃ O ₂
292839	CO2Et	6-MeO-4-quinolyl-NHCO2	3RS,4SR	C ₂₆ H ₃₇ N ₃ O ₅

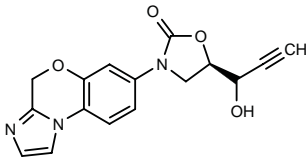
SOURCE – GlaxoSmithKline.

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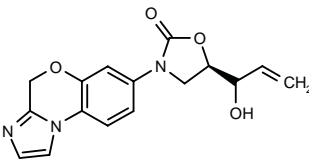
293305

5(*R*)-(1-Hydroxy-2-propynyl)-3-(4*H*-imidazo[2,1-*c*][1,4]-benzoxazin-7-yl)oxazolidin-2-one



C16 H13 N3 O4; Mol wt: 311.2957

ACTION – Oxazolidinone antibacterial agent active against Gram-positive bacteria such as *Staphylococcus aureus* 133 (MIC = 1 µg/ml), as well as certain Gram-negative bacteria, mycobacteria, corynebacteria, *Haemophilus influenzae* and anaerobes. Another compound from this series of hydroxymethyl-substituted oxazolidinone derivatives is:



293306: C16 H15 N3 O4

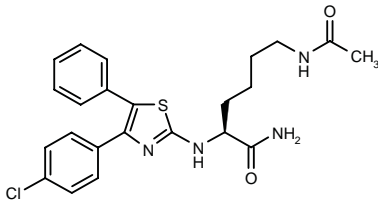
SOURCE – Bayer.

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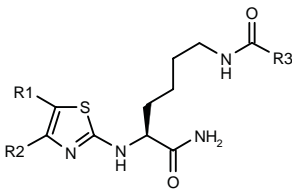
293450

N^ε-Acetyl-*N*^α-[4-(4-chlorophenyl)-5-phenylthiazol-2-yl]-L-lysineamide

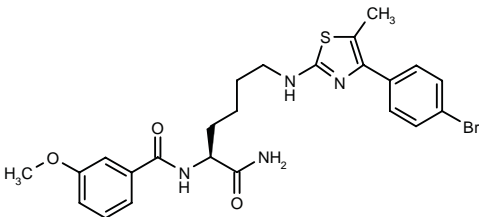


C23 H25 Cl N4 O2 S; Mol wt: 456.9955

ACTION – Antimicrobial agent demonstrated to be active *in vitro* against *Streptococcus pyogenes*. A representative compound from a series of thiazole derivatives prepared by combinatorial techniques, wherein the following are also included:



Compound	R1	R2	R3	Formula
293451	Ph	4-Cl-Ph	3-CF3-Ph	C ₂₉ H ₂₆ ClF ₃ N ₄ O ₂ S
293452	Me	4-Br-Ph	3-MeO-Ph	C ₂₄ H ₂₇ BrN ₄ O ₃ S
293453	Ph	4-Cl-Ph	4-I-Ph	C ₂₈ H ₂₆ ClIN ₄ O ₂ S
293455	Me	4-Br-Ph	(CH ₂) ₄ Ph	C ₂₇ H ₃₃ BrN ₄ O ₂ S
293456	Me	4-Br-Ph	CH ₂ CH(Me)Ph	C ₂₆ H ₃₁ BrN ₄ O ₂ S
293457	H	CH ₂ CO ₂ Me	CH ₂ OEt	C ₁₆ H ₂₆ N ₄ O ₅ S
293458	H	2-Naph	9H-xanthen-9-yl	C ₃₃ H ₃₀ N ₄ O ₃ S



293459: C24 H27 Br N4 O3 S

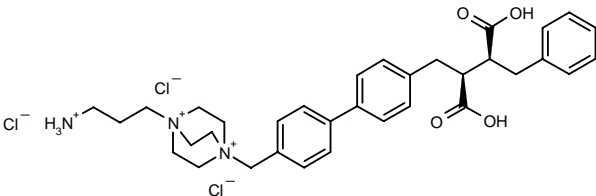
SOURCE – Trega Biosciences.

REFERENCES

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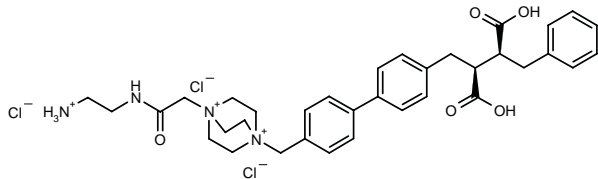
293727

1-(3-Ammoniopropyl)-4-[4'-[2(*S*),3(*S*)-dicarboxy-4-phenylbutyl]biphenyl-4-ylmethyl]-1,4-diazoniabicyclo[2.2.2]-octane trichloride



C34 H44 Cl3 N3 O4; Mol wt: 665.0976

ACTION – Imipenem (IMP)-1 metallo-β-lactamase inhibitor, proven to reverse IMP-1-mediated resistance. Compound at 12.5 μM induced at least a 4-fold reduction in imipenem MICs against 5 of 6 imipenem-susceptible clinical isolates. When combined with compound, 15 of 18 imipenem-resistant strains were inhibited by clinically achievable levels of imipenem (8 μg/ml or less). Compound did not have intrinsic antibacterial activity. Another succinic acid derivative is:



293728: C35 H45 Cl3 N4 O5

SOURCE – Merck & Co.

REFERENCES

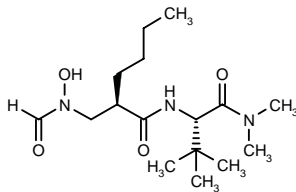
1. Huber, J.L. et al. *Inhibition of IMP-1 metallo-beta-lactamase in clinical isolates by two succinic acid derivatives*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1226.

BB-3497

293511

*N*²-[2(*R*)-(*N*-Formyl-*N*-hydroxyaminomethyl)hexanoyl]-*N*¹,*N*¹-dimethyl-*L*-*tert*-leucinamide

2(*R*)-Butyl-*N*-formyl-*N*-hydroxy-β-alanyl-*N,N*,3-trimethyl-*L*-valinamide



C16 H31 N3 O4; Mol wt: 329.4379

ACTION – Antibacterial agent, a selective inhibitor of bacterial peptide deformylase (PDF; IC₅₀ = 7 nM against enzyme from *Escherichia coli*). Compound showed antibacterial activity against *E. coli* and moderate activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), and its mode of action was primarily bacteriostatic. It exhibited a good pharmacokinetic profile in mice, with a C_{max} of 23 μg/ml and an AUC of 23 μg.ml/h after a dose of 100 mg/kg p.o. In a mouse model of septicemia induced by *S. aureus*, compound showed good efficacy, with a median effective dose below 10 mg/kg p.o.

SOURCE – British Biotech.

REFERENCES

1. Hunter, M.G. et al. (British Biotech Pharmaceuticals Ltd.) *Antibacterial agents*. WO 9939704.
2. Baker, P. et al. *X-Ray crystal structures of the inhibitors actinonin and BB-3497 bound to E.coli peptide deformylase*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-2178.

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1. Hinks, J.D. et al. (SmithKline Beecham plc) *Carbamoyloxy derivs. of mutuline and their use as antibacterials*. EP 0874809, EP 0934316, JP 2000503642, JP 2000515532, US 6121281, WO 9725309, WO 9805659.

2. Rittenhouse, S.F. et al. *In vitro activity of the novel pleuromutilin SB-264128 against organisms associated with respiratory tract infection*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-2199.

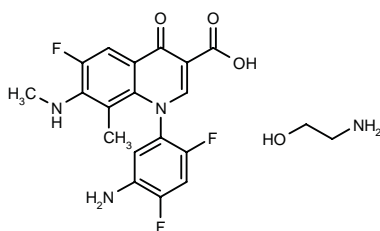
3. Satterfield, J. et al. *In vivo efficacy of the novel oral pleuromutilin, SB-264128*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-2198.

WQ-3402

293852

1-(5-Amino-2,4-difluorophenyl)-6-fluoro-8-methyl-7-(methylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethanolamine salt

WQ-2944 (free acid)



C18 H14 F3 N3 O3 . C2 H7 N O; Mol wt: 438.4039

ACTION – Quinolone antibacterial agent with excellent oral activity against murine systemic infections, giving ED₅₀ values of 11 and 19 mg/kg, respectively, against infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, versus ED₅₀ values of 59 and 26 mg/kg, respectively, for levofloxacin; it was also effective against respiratory tract infections, affording significant reductions in bacterial counts in lungs at the dose of 50 mg/kg in animals with infections caused by *Streptococcus pneumoniae*. The free acid, WQ-2944, exhibited broad-spectrum antibacterial activity against both Gram-positive and Gram-negative strains including *S. aureus*, *Enterococcus faecalis*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae* and *P. aeruginosa* (MIC < 0.004-1 µg/ml). WQ-2944 was up to 10-fold more potent than trovafloxacin against Gram-positive bacteria, and it was at least as active as ciprofloxacin against Gram-negative bacteria. Moreover, WQ-2944 exhibited excellent activity versus clinical isolates including MRSA, ciprofloxacin-resistant MRSA, *S. pneumoniae* and *P. aeruginosa* (geometric mean MICs = 0.009, 3.43, 0.065 and 0.30 µg/ml, respectively), as well as against vancomycin-resistant enterococci (geometric mean MICs = 0.12-5.38 µg/ml). No phototoxicity was seen in mice given a dose of 80 mg/kg i.v.

SOURCE – Wakunaga.

REFERENCES

1. Sakae, N. et al. (Wakunaga Pharmaceutical Co., Ltd.) *Novel pyridonecarboxylic acid derivs. or salts thereof and drugs containing the same as the active ingredient*. EP 0945435, US 6136823, WO 9823592.

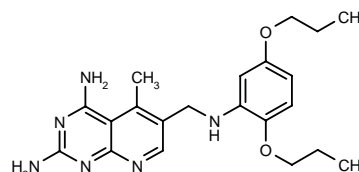
2. Kuramoto, Y. et al. *Structure-activity relationships of novel acidic, 7-amino or 7-alkylamino-1-(5-amino-2,4-difluorophenyl)-8-methylquinolones*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1504.

ANTIMYCOBACTERIAL AGENTS

SRI-20094

293513

6-(2,5-Dipropoxyphenylaminomethyl)-5-methylpyrido-[2,3-d]pyrimidine-2,4-diamine



C21 H28 N6 O2; Mol wt: 396.4922

ACTION – Antimycobacterial agent, a selective inhibitor of mycobacterial dihydrofolate reductase (DHFR; IC₅₀ = 1 nM) with over 7,000-fold selectivity relative to human DHFR. In monocytic MM6 cells infected with *Mycobacterium avium*, compound decreased colony-forming units (MIC < 0.13 µg/ml) without inducing a significant decrease in cell viability.

SOURCE – Southern Research Institute, Birmingham, AL (US).

REFERENCES

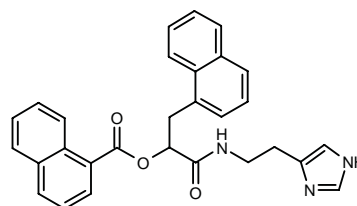
1. Suling, W.J. et al. *Antimycobacterial activities of 2,4-diamino-5-deazapteridine derivatives and effects on mycobacterial dihydrofolate reductase*. Antimicrob Agents Chemother 2000, 44(10): 2784.

2. Suling, W.J. et al. *Selective inhibition of M. avium dihydrofolate reductase (DHFR) and intracellular efficacy of 2,4-diamino-5-deaza-pteridines*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-2183.

ANTIFUNGAL AGENTS

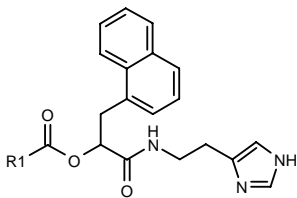
293801

Naphthalene-1-carboxylic acid 1-[N-[2-(1H-imidazol-4-yl)ethyl]carbamoyl]-2-(1-naphthyl)ethyl ester



C29 H25 N3 O3; Mol wt: 463.5345

ACTION – Antifungal agent that acts by inhibiting fungal type I protein geranylgeranyltransferase (GGTase I), as demonstrated by an IC₅₀ value of 11 nM against enzyme from *Candida albicans* ATCC90028. Other exemplified compounds from this series of imidazole derivatives include the following:



Compound	R1	Formula
293803	9H-xanthen-9-yl	C ₃₂ H ₂₇ N ₃ O ₄
293804	2-Naph	C ₂₈ H ₂₅ N ₃ O ₃

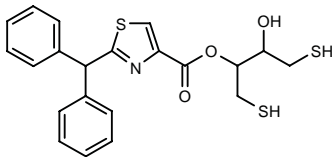
SOURCE – Banyu.

REFERENCES

1. Ohkubo, M. et al. (Banyu Pharmaceutical Co., Ltd.) *Type I protein geranylgeranyl transferase inhibitors*. JP 2000204078.

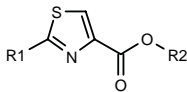
293805

2-(Diphenylmethyl)thiazole-4-carboxylic acid 2-hydroxy-3-sulfanyl-1-(sulfanylmethyl)propyl ester



C21 H21 N O3 S3; Mol wt: 431.5989

ACTION – Antifungal agent that acts by inhibiting fungal type I protein geranylgeranyltransferase (GGTase I), as demonstrated by an IC₅₀ value of 7.9 nM against enzyme from *Candida albicans* ATCC90028. Other exemplified compounds from this series of thiazole derivatives include the following:



Compound	R1	R2	Formula
293807	1,4-benzodioxan-2-yl	CH(CH2SH)CH(OH)CH2SH	C ₁₆ H ₁₇ NO ₅ S ₃
293808	1,4-benzodioxan-2-yl	3-SH-cyclohexyl	C ₁₈ H ₁₉ NO ₄ S ₂
293810	1,2,3,4-tetrahydro-1-Naph	CH(CH2SH)CH(OH)CH2SH	C ₁₈ H ₂₁ NO ₃ S ₃
293811	2-i-PrO-PhOCH2	CH(CH2SH)CH(OH)CH2SH	C ₁₈ H ₂₃ NO ₅ S ₃
293812	9-fluorenyl-CH2	3-SH-cyclohexyl	C ₂₄ H ₂₃ NO ₂ S ₂

SOURCE – Banyu.

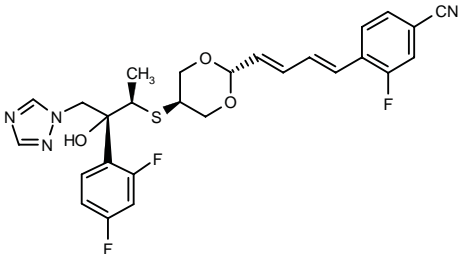
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R-120758

293411

4-[4-[*trans*-5-[2(*R*)-(2,4-Difluorophenyl)-2-hydroxy-1(*R*)-methyl-3-(1*H*-1,2,4-triazol-1-yl)propylsulfanyl]-1,3-dioxan-2-yl]-1(*E*),3(*E*)-butadienyl]-3-fluorobenzonitrile



C27 H25 F3 N4 O3 S; Mol wt: 542.5795

ACTION – Antifungal agent with broad-spectrum *in vitro* activity against clinically important fungi including *Candida albicans* (MIC₉₀ = 0.008 µg/ml or less), *Candida glabrata* (MIC₉₀ = 0.25 µg/ml), *Candida tropicalis* (MIC₉₀ = 0.016 µg/ml), *Candida parapsilosis* (MIC₉₀ = 0.06 µg/ml), *Candida krusei* (MIC₉₀ = 0.25 µg/ml), *Cryptococcus neoformans* (MIC₉₀ = 0.008 µg/ml or less), *Aspergillus fumigatus* (MIC₉₀ = 0.06 µg/ml) and *Aspergillus flavus* (MIC₉₀ = 0.063 µg/ml), as well as against *C. albicans* with low susceptibility to fluconazole (MIC = 0.016-0.5 µg/ml). Compound demonstrated consistently superior activity versus amphotericin B, fluconazole and itraconazole. Pharmacokinetic experiments demonstrated excellent oral absorption (bioavailability of 98.3% in rats, 71.8% in monkeys) and extensive tissue distribution. *In vivo* in murine systemic infections caused by *C. albicans*, *A. fumigatus*, *A. flavus* and *C. neoformans*, compound given once daily orally for 10 days delayed death with ED₅₀ values of 0.409, 2.38, 3.12 and 3.12 mg/kg, respectively; its efficacy was comparable to fluconazole against *C. albicans* but superior to both fluconazole and itraconazole against *Aspergillus* spp. and *C. neoformans*. Safety studies demonstrated no lethality after single oral doses of up to 2000 mg/kg in rats, dogs and monkeys, and no severe toxicity was seen after 14-day repeated oral doses in rats; no signs of genotoxicity were observed.

SOURCE – Sankyo.

REFERENCES

1. Oida, S. et al. (Sankyo Co., Ltd.) *Triazole antifungal agent*. EP 0841327, JP 1996333350, US 5977152, WO 9631491.

2. Fothergill, A.W. et al. *Comparison of the investigational azole R-120758 to amphotericin B, fluconazole, and itraconazole against 150 Aspergillus spp.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1089.

3. Kamai, Y. et al. *R-120758, a novel triazole antifungal agent: In vitro antifungal activity.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1088.

4. Kamai, Y. et al. *R-120758, a novel triazole antifungal agent: In vivo antifungal activity.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1091.

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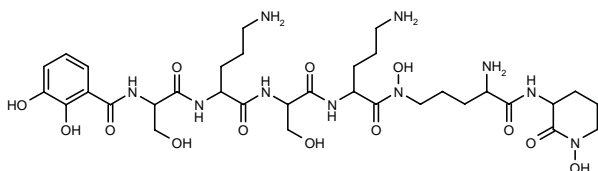
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S-213L

293788

2-Amino-5-[N-(2,3-dihydroxybenzoyl-DL-seryl-DL-ornithyl)-DL-seryl-DL-ornithyl]-N-hydroxyamino]-N-(1-hydroxy-2-oxopiperidin-3-yl)pentanamide



C33 H54 N10 O13; Mol wt: 798.8466

ACTION – Antibiotic isolated from *Streptomyces* sp. POL-1285 (FERM P-17108) with antifungal, antibacterial, antiviral and antitumor activity. For example, antifungal activity was demonstrated against *Candida glabrata* (MIC = 6.25 µg/ml), *Trichophyton mentagrophytes* (MIC = 12.5-25 µg/ml) and *Trichophyton rubrum* (MIC = 25 µg/ml), and antibacterial activity was seen against *Pseudomonas aeruginosa* IFO 3445 (MIC = 12.5 µg/ml), *Proteus vulgaris* HX19 (MIC = 12.5 µg/ml) and *Micrococcus luteus* ATCC 9341 (MIC = 6.25 µg/ml).

SOURCE – Pola Chemical.

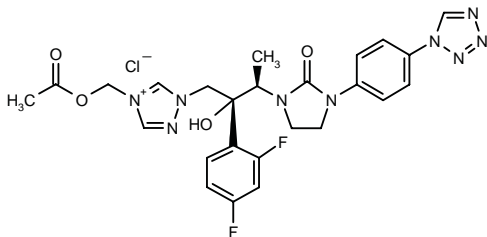
REFERENCES

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TAK-457^{2,3,7,9}

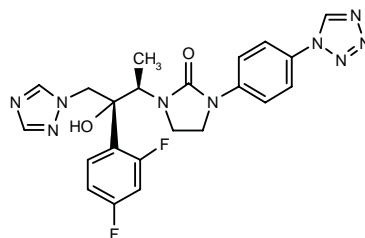
293410

4-(Acetoxymethyl)-1-[2(R)-(2,4-difluorophenyl)-2-hydroxy-3(R)-[2-oxo-3-[4-(1H-tetrazol-1-yl)phenyl]imidazolidin-1-yl]butyl]-1H-1,2,4-triazol-4-ium chloride



C25 H26 Cl F2 N9 O4; Mol wt: 589.9884

ACTION – Water-soluble prodrug of the potent antifungal triazole **TAK-456**. The active compound showed potent *in vitro* antifungal activity, superior to fluconazole and comparable to itraconazole, against azole-susceptible *Candida albicans* (MIC = 0.008-0.03 µg/ml), azole-resistant *C. albicans* (MIC = 2 µg/ml), *Cryptococcus neoformans* (MIC = 0.5 µg/ml) and *Aspergillus fumigatus* (MIC = 0.5 µg/ml). TAK-456 acts by inhibiting fungal ergosterol biosynthesis, as demonstrated in *C. albicans* and *A. fumigatus* (IC₅₀ = 0.003 and 0.010 µg/ml, respectively). In a moderately severe pulmonary aspergillosis infection model in neutropenic mice, the prodrug (10 mg/kg/day i.v. x 5) and amphotericin B (1 mg/kg i.v.), but not voriconazole or fluconazole, prolonged survival, and in a severe pulmonary aspergillosis model, the prodrug was more effective than amphotericin B in prolonging survival. Selected as a clinical candidate for the treatment of candidemia and pulmonary aspergillosis.



TAK-456 [293408]:^{1,2,4-9} C22 H21 F2 N9 O2

SOURCE – Takeda.

REFERENCES

1. Hashimoto, H. et al. (Takeda Chemical Industries, Ltd.) *Process for producing cyclic amide cpd*. WO 0034267.

2. Ito, K. et al. (Takeda Chemical Industries, Ltd.) *Intermediates for the synthesis of imidazolone and imidazolidinone derivs., and their preparation method*. JP 2000063364.

3. Itoh, K. et al. (Takeda Chemical Industries, Ltd.) *Azole cpds., their production and their use*. EP 0973768, JP 1999228548, JP 2000198773, WO 9843970.

4. Itoh, K. et al. (Takeda Chemical Industries, Ltd.) *Azole cpds., their production and use*. EP 0809640, JP 1997183769, WO 9625410.

5. Kitazaki, T. et al. (Takeda Chemical Industries, Ltd.) *Triazole derivs. and their production*. EP 0884311.

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8. Kitazaki, T. et al. *Optically active antifungal azoles. X. Synthesis and antifungal activity of N-[4-(azolyl)phenyl] and N-[4-(azolylmethyl)phenyl]-N'[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-azolones*. Chem Pharm Bull 2000, 48(12): 1935.

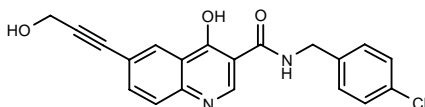
9. Kitazaki, T. et al. *TAK-456 and the water-soluble prodrug TAK-457, new antifungal triazoles: Synthesis and in vitro antifungal activity*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1085.

ANTIVIRAL DRUGS

PNU-181128¹⁻⁴

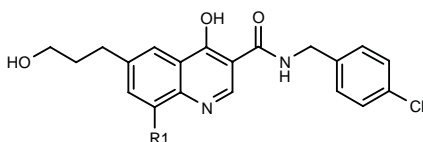
290722

N-(4-Chlorobenzyl)-4-hydroxy-6-(3-hydroxy-1-propynyl)-quinoline-3-carboxamide



C₂₀ H₁₅ Cl N₂ O₃; Mol wt: 366.8025

ACTION – Broad-spectrum inhibitor of DNA polymerase from herpesviruses including human cytomegalovirus (HCMV; IC₅₀ = 0.95 μM), herpes simplex virus type 1 (HSV-1; IC₅₀ = 0.72 μM) and varicella-zoster virus (VZV; IC₅₀ = 0.19 μM), devoid of activity against human α, δ and γ DNA polymerases (IC₅₀ > 20 μM). Compound exhibited strong antiviral activity against HSV-1, VZV, HCMV and simian varicella virus (IC₅₀ = 7.4, 0.7, 4.7 and 2.5 μM, respectively), as well as against ganciclovir- and cidofovir-resistant HCMV (IC₅₀ = 0.1-0.6 μM). Other related 4-hydroxyquinolines are:



Compound	R1	Formula
PNU-180784 [278256] ^{*,1,2,4}	F	C ₂₀ H ₁₈ ClFN ₂ O ₃
PNU-181465 [278260] ^{**,1-4}	H	C ₂₀ H ₁₉ ClN ₂ O ₃

SOURCE – Pharmacia.

REFERENCES

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2. Brideau, R.J. et al. *Broad spectrum anti-herpes virus cell cultured activity of novel 4-hydroxyquinolines which target the viral polymerase*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1856.

3. Huang, A. et al. *4-Hydroxyquinoline-3-carboxamides as inhibitors of herpesvirus DNA polymerases*. 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst A-11.

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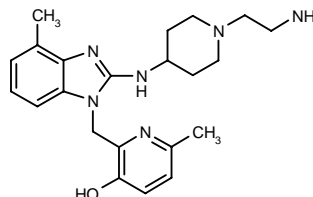
*Identified compound **278256** (see **278255**) Drug Data Rep 1999, 021(08): 0716.

Identified compound **278260 (see **278255**) Drug Data Rep 1999, 021(08): 0716.

R-170591

293399

2-[2-[1-(2-Aminoethyl)piperidin-4-ylamino]-4-methyl-1*H*-benzimidazol-1-ylmethyl]-6-methylpyridin-3-ol



C₂₂ H₃₀ N₆ O; Mol wt: 394.5200

ACTION – Antiviral agent active against respiratory syncytial virus (RSV; IC₅₀ = 150 pM), with an antiviral potency that exceeds almost 100,000-fold that of ribavirin (IC₅₀ = 10 μM). Compound was active against human and bovine RSV and in infected human respiratory tract cell lines. No cytotoxicity was seen at up to 100 μM. In cotton rats, compound given i.p. or by inhalation exhibited > 90% reduction in RSV titers in lung and bronchoalveolar lavage fluid (BALF). It showed a dual mode of action: inhibition of virus–cell fusion early in the infection cycle and inhibition of cell–cell fusion at the end of the replication cycle. A candidate for further development.

SOURCE – Janssen.

REFERENCES

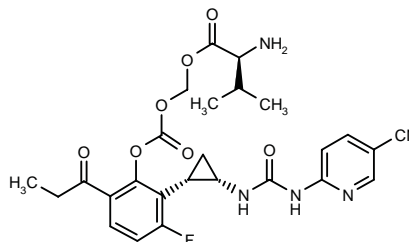
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AIDS MEDICINES

293490

L-Valine 2-[(1*S*,2*S*)-2-[*N*³-(5-cyanopyridin-2-yl)ureido]-cyclopropyl]-3-fluoro-6-propionylphenoxycarbonyloxy-methyl ester



C₂₆ H₂₈ F N₅ O₇; Mol wt: 541.5332

ACTION – Prodrug of a known non-nucleoside HIV-1 reverse transcriptase inhibitor* with an improved pharmacokinetic profile. When the compound was orally administered to rats at 0.027 mmol/kg, it gave a C_{max} of 1.5 μM and a bioavailability of 70%, with sustained plasma levels of the active metabolite well above the ED₅₀ for HIV-1.

SOURCE – Medivir.

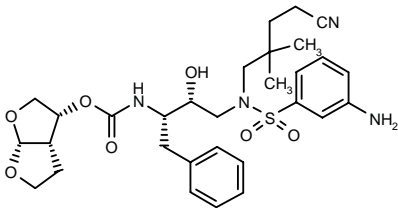
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*See 278983 Drug Data Rep 1999, 021(10): 0913.

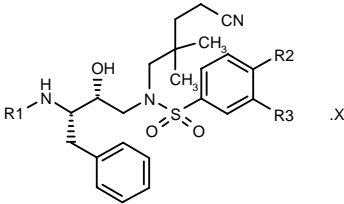
293668

N-[3-[N-(3-Aminophenylsulfonyl)-N-(4-cyano-2,2-dimethylbutyl)amino]-1 (S)-benzyl-2 (R)-hydroxypropyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester

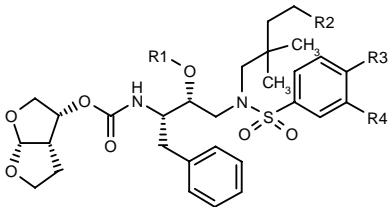


C30 H40 N4 O7 S; Mol wt: 600.7330

ACTION – Anti-HIV agent that acts by inhibiting HIV-1 and HIV-2 aspartyl proteases. When tested *in vitro* against HIV-1 protease, the compound gave a $K_i < 1$ nM. Anti-HIV activity was demonstrated in MT-4 cells, with an IC_{50} value of 0.1 μ M or less. Other exemplified sulfonamide derivatives include the following:



Compound	R1	R2	R3	X	Formula
293669	t-BuOCO	H	NHMe		C ₂₉ H ₄₂ N ₄ O ₅ S
293670	H	-OCH2O-		CF3CO2H	C ₂₄ H ₃₁ N ₃ O ₅ S .C ₂ H ₃ O ₂
293671	1,3-dioxan-5-yl- -OCO	OH	H		C ₂₈ H ₃₇ N ₃ O ₅ S



Compound	R1	R2	R3	R4	Formula
293672	PO(OCH2Ph)2	CN		-OCH2O-	C ₄₆ H ₅₂ N ₃ O ₁₂ PS
293675	PO3(NH4)2	CN	H	NHMe	C ₃₁ H ₄₉ N ₆ O ₁₀ PS
293678	H	2-Me- 1,3-dioxolan-2-yl	H	NHMe	C ₃₄ H ₄₉ N ₃ O ₅ S
293680	H	Ac		-OCH2O-	C ₃₂ H ₄₂ N ₂ O ₁₀ S
293681	H	CH2OCONHMe		-OCH2O-	C ₃₃ H ₄₅ N ₃ O ₁₁ S
293682	H	CH2NHCO2Et		-OCH2O-	C ₃₄ H ₄₇ N ₃ O ₁₁ S
293683	H	CH2CH2- NHCO2Et		-OCH2O-	C ₃₅ H ₄₉ N ₃ O ₁₁ S

SOURCE – Vertex.

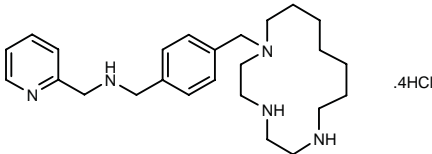
REFERENCES

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AMD-8664

293467

N-(2-Pyridinylmethyl)-N-[4-(1,4,7-triazacyclotetradecan-1-ylmethyl)benzyl]amine tetrahydrochloride



C25 H39 N5 . 4HCl; Mol wt: 555.4617

ACTION – Antiviral agent for AIDS, an orally active antagonist of the chemokine receptor CXCR4 with potent activity against laboratory strains of HIV-1 ($EC_{50} = 32$ ng/ml in MT-4 cells and peripheral blood mononuclear cells); the compound was active against T-tropic (CXCR4) clinical isolates ($EC_{50} = 69.4$ ng/ml) and dual T/M-tropic (CXCR4/CCR5) isolates ($EC_{50} = 9$ ng/ml), but not against M-tropic (CCR5) strains of HIV, and it was not toxic to MT-4 cells at concentrations over 100 μ g/ml. It showed good oral absorption in rabbits, with a bioavailability of 87.8%, and was well tolerated in rats and rabbits.

SOURCE – AnorMED.

REFERENCES

1. Bridger, G. et al. (AnorMED Inc.) *Chemokine receptor binding heterocyclic cpds*. WO 0056729.

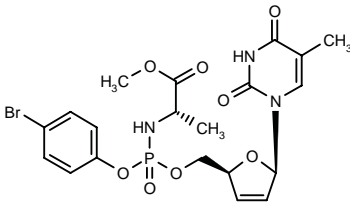
2. Macfarland, R.T. et al. *An orally bioavailable CXCR4 antagonist for inhibition of HIV replication*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1845.

HI-113*

269049

5'-O-[(4-Bromophenoxy)(O-methyl-L-alanino)phosphoryl]-3'-deoxy-2',3'-didehydrothymidine

d4T-pBPMAP



C20 H23 Br N3 O8 P; Mol wt: 544.2927

ACTION – Antiviral agent for AIDS, an arylphosphate derivative of stavudine (d4T) with potent anti-HIV activity in HIV-infected peripheral blood mononuclear cells (PBMCs) and in thymidine kinase (TK)-deficient CEM cells (IC_{50} = 22 and 44 nM, respectively). Compound was found to inhibit HIV reverse transcriptase both in PBMCs and in TK-deficient CEM cells (IC_{50} = 42 and 57 nM, respectively). No cytotoxicity was seen at up to 10 μ M in both types of cells. In mice, compound is metabolized to two active compounds –d4T and Ala-d4T-MP– following either i.v. injection or oral administration, and both metabolites showed favorable pharmacokinetics, particularly as regards their prolonged elimination half-lives compared to the parent compound.

SOURCE – Parker Hughes Institute, Roseville, MN (US).

REFERENCES

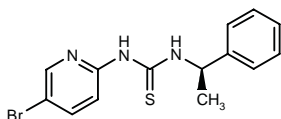
1. Uckun, F.M. and Vig, R. (Parker Hughes Institute) *Aryl phosphate derivs. of d4T having anti-HIV activity*. US 6030957, WO 0000501.
2. Uckun, F.M. et al. *Pharmacokinetics and metabolism of HI-113, an aryl phosphate derivative of D4T in mice*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abstr 1251.
3. Venkatachalam, T.K. et al. *Enhancing effects of a mono-bromo substitution at the para position of the phenyl moiety on the metabolism and anti-HIV activity of d4T-phenyl methoxyalaninyl phosphate derivatives*. Bioorg Med Chem Lett 1998, 8(22): 3121.
4. Vig, R. et al. *D4T-5'-[p-Bromophenyl methoxyalaninyl phosphate] as a potent and non-toxic anti-human immunodeficiency virus agent*. Antivir Chem Chemother 1998, 9(5): 445.

*Identified compound **269049** Drug Data Rep 1999, 021(01): 0060.

(R)-HI-511

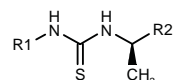
294232

N-(5-Bromopyridin-2-yl)-*N'*-[1(*R*)-phenylethyl]thiourea



C₁₄ H₁₄ Br N₃ S; Mol wt: 336.2556

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor (NNRTI; IC_{50} = 1.6 μ M) with the ability to inhibit HIV-1 replication in human peripheral blood mononuclear cells (IC_{50} = 0.01 μ M). Compound was more active than nevirapine or delavirdine against the NNRTI-resistant HIV-1 strain A17 with the Y181C mutation (IC_{50} = 0.01, > 100 and 50 μ M, respectively) and the multidrug-resistant HIV strain V106A (IC_{50} = 0.005, 5 and 0.4 μ M, respectively). It was also able to inhibit the highly NNRTI-resistant HIV-1 strain A17 variant with Y181C plus K103N mutations in RT, with an IC_{50} value of 2.7 μ M compared to an IC_{50} > 100 μ M for nevirapine and delavirdine. Other related thioureas are:



Compound	R1	R2	Formula
(R)-HI-509 [294230]	5-Br-2-Pyr	cyclohexyl	C ₁₄ H ₂₀ BrN ₃ S
(R)-HI-510 [294231]	5-Cl-2-Pyr	cyclohexyl	C ₁₄ H ₂₀ ClN ₃ S
(R)-HI-512 [294233]	5-Cl-2-Pyr	Ph	C ₁₄ H ₁₄ ClN ₃ S
(R)-HI-513 [294234]	2-thiazolyl	cyclohexyl	C ₁₂ H ₁₈ N ₃ S ₂

SOURCE – Parker Hughes Institute, Roseville, MN (US).

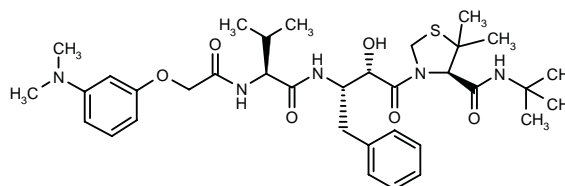
REFERENCES

1. Venkatachalam, T.K. et al. *Stereochemistry of halopyridyl and thiazolyl thiourea compounds is a major determinant of their potency as nonnucleoside inhibitors of HIV-1 reverse transcriptase*. Bioorg Med Chem Lett 2000, 10(18): 2071.

JE-2178*

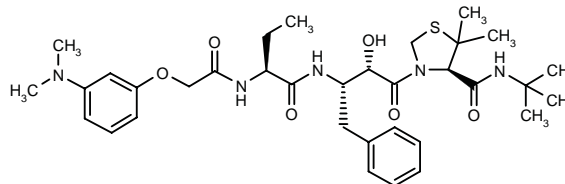
270447

N-*tert*-Butyl-3-[3(*S*)-[*N* α -[2-[3-(dimethylamino)phenoxy]acetyl]-*L*-valylamino]-2(*S*)-hydroxy-4-phenylbutyryl]-5,5-dimethylthiazolidine-4(*R*)-carboxamide



C₃₅ H₅₁ N₅ O₆ S; Mol wt: 669.8829

ACTION – Antiviral agent for AIDS, a potent and selective HIV protease inhibitor (IC_{50} = 0.318 nM) with antiviral activity in CEM-SS cells (IC_{50} = 15 nM). Compound exhibited a good pharmacokinetic profile in rats with a long plasma half-life (> 60 min) and excellent bioavailability (89%) after i.d. administration. Within this series of tripeptide-based HIV protease inhibitors, another compound is:



JE-2179 [270450]:** C₃₄ H₄₉ N₅ O₆ S

SOURCE – Japan Energy.

REFERENCES

1. Takaku, H. et al. (Japan Energy Corp.) *Novel tripeptide cpds. and anti-AIDS drugs*. EP 0900566, WO 9829118.
2. Mimoto, T. et al. *Structure-activity relationship of orally potent tripeptide-based HIV protease inhibitors containing hydroxymethylcarbonyl isostere*. Chem Pharm Bull 2000, 48(9): 1310.

*Identified compound **270447** Drug Data Rep 1999, 021(01): 0062.

Identified compound **270450 (see **270447**) Drug Data Rep 1999, 021(01): 0062.

MK-944a

284604

Combination of indinavir sulfate and L-756423

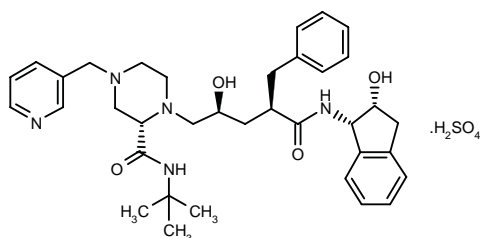
Indinavir Sulfate*

Prop INN[®]; USAN

199183

2(R)-Benzyl-5-[2(S)-(N-tert-butylcarbamoyl)-4-(3-pyridylmethyl)piperazin-1-yl]-4(S)-hydroxy-N-[2(R)-hydroxyindan-1(S)-yl]pentanamide sulfate (1:1)

Crixivan[®]

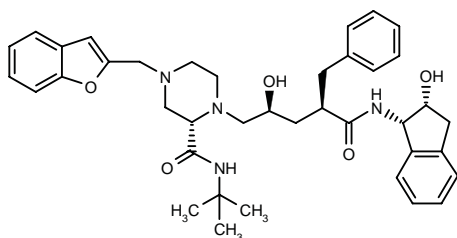


C36 H47 N5 O4 . H2 O4 S; Mol wt: 711.8761

L-756423

285239

2(R)-Benzyl-5-[4-(2-benzo[b]furanyl)-2(S)-(N-tert-butylcarbamoyl)piperazin-1-yl]-4(S)-hydroxy-N-[2(R)-hydroxyindan-1(S)-yl]pentanamide



C39 H48 N4 O5; Mol wt: 652.8312

ACTION – Anti-HIV agent, a combination of the protease inhibitors L-756423 ($K_i = 0.049$ nM against wild-type HIV-1 protease; $IC_{50} = 0.18$ nM) and indinavir sulfate. At concentrations up to $10 \mu\text{M}$ it did not significantly inhibit a variety of other proteases including human cathepsin D, porcine pepsin and human gastric chymosin, and it did not inhibit cytochrome P-450 isozymes. Compound was found to be more effective than indinavir *in vitro* in suppressing the spread of acute HIV-1 infection in MT-4 cells and its potency was only minimally affected by the addition of human serum, α_1 -acid glycoprotein or fetal bovine serum. Pharmacokinetic studies in rats, dogs and monkeys demonstrated a longer half-life than indinavir and low renal excretion. In phase I studies in healthy volunteers given combination capsules, pharmacokinetics were similar to those obtained with the component drugs administered separately. Combination is now under clinical evaluation using once- and twice-daily dosing regimens.

SOURCE – Merck & Co.

REFERENCES

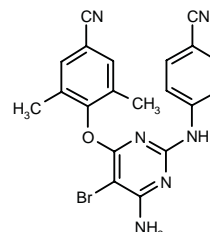
1. Askin, D. et al. (Merck & Co., Inc.) *Sulfate salt of an HIV protease inhibitor having an improved oral absorption and bioavailability*. EP 0986554, JP 2000513747, US 6071916, WO 9854178.
2. Vacca, J.P. et al. (Merck & Co., Inc.) *Combination therapy for the treatment of AIDS*. WO 9925352.
3. Deutsch, P. et al. *Pharmacokinetics and tolerability of MK-944A, a combination of a new HIV protease inhibitor with indinavir, in phase I studies*. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 506.
4. Dorsey, B.D. et al. *Identification of MK-944a: A second clinical candidate from the hydroxylaminepentanamide isostere series of HIV protease inhibitors*. J Med Chem 2000, 43(18): 3386.
5. Rose, M.J. et al. *Determination of L-756423, a novel HIV protease inhibitor, in human plasma and urine using high-performance liquid chromatography with fluorescence detection*. J Chromatogr B - Biomed Sci Appl 1999, 732(2): 425.
6. Rose, M.J. et al. *High-throughput simultaneous determination of the HIV protease inhibitors indinavir and L-756423 in human plasma using semi-automated 96-well solid phase extraction and LC-MS/MS*. J Pharm Biomed Anal 2000, 24(2): 291.
7. *Promising late-stage compounds discussed at Merck & Co. analyst meeting last week*. DailyDrugNews.com (Daily Essentials) 1999, Dec 16.

*Drug Data Rep 1996, 018(05): 0454.

R-165335/TMC-125*

290137

4-[6-Amino-5-bromo-2-(4-cyanophenylamino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile



C20 H15 Br N6 O; Mol wt: 435.2835

ACTION – Antiviral agent for AIDS, a highly potent and noncytotoxic inhibitor of wild-type HIV-1 ($IC_{50} = 1.4$ nM; $IC_{90} = 2.9$ nM; $CC_{50} > 100 \mu\text{M}$; selectivity index $> 71,428$). The anti-HIV potency of the compound was not significantly affected by human serum proteins and it was only slightly (15%) degraded in the presence of human liver microsomes. A third-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), it inhibited 98% of over 2,000 recent clinical isolates and 97% of approximately 1,000 NNRTI-resistant strains with an IC_{50} below 100 nM, being significantly more effective than efavirenz against the resistant strains. Considered an excellent candidate for clinical development.

SOURCES – Janssen; Tibotec.

REFERENCES

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3. Andries, K. et al. *R165335-TMC125, a novel non nucleoside reverse transcriptase inhibitor (NNRTI) with nanomolar activity against NNRTI resistant HIV strains*. AIDS 2000, 14(Suppl. 4): Abst PL4.5.

4. de Béthune, M.-P. et al. *R165335-TMC125, a third generation nonnucleoside reverse transcriptase inhibitor (NNRTI), inhibits 97% of more than 1000 recombinant NNRTI resistant HIV clinical isolates with an IC50 below 100 nM.* AIDS 2000, 14(Suppl. 4): Abst P2.

5. De Bethune, M.P. et al. *R165335-TMC125, a third generation non nucleoside reverse transcriptase inhibitor (NNRTI), inhibits 98% of more than 2,000 recombinant HIV clinical isolates at 100 nM.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1841.

*Identified compound **290137** Drug Data Rep 2000, 022(09): 0823.

TREATMENT OF PROTOZOAL DISEASES

MAb R217

294144

Monoclonal antibody to EBA-175

ACTION– Monoclonal antibody that inhibits the binding of the *Plasmodium falciparum* erythrocyte-binding protein EBA-175 to erythrocytes, as demonstrated by > 90% inhibition of the binding of [³⁵S]-methionine-labeled EBA-175 to erythrocytes. This antibody also blocked merozoite invasion in the homologous FVO (83%) and in the heterologous 3D7 (39%) strains. Potentially useful for the treatment, diagnosis and prevention of malaria. Other exemplified antibodies to EBA-175 are:

MAb R215 [294145]

MAb R256 [294146]

SOURCE – EntreMed.

REFERENCES

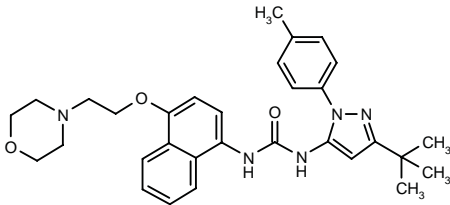
1. Narum, D.L. and Sim, K.L. (EntreMed, Inc.) *Anti-Plasmodium compsns. and methods of use.* WO 0052056.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

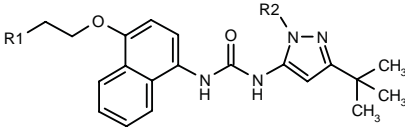
292897

N-[3-*tert*-Butyl-1-(4-methylphenyl)-1*H*-pyrazol-5-yl]-*N*'-[4-[2-(4-morpholinyl)ethoxy]naphthalen-1-yl]urea



C31 H37 N5 O3; Mol wt: 527.6653

ACTION – Antiinflammatory agent that acts by inhibiting inflammatory cytokines such as IL-1 and TNF and is potentially useful for the treatment of rheumatoid arthritis, multiple sclerosis, Guillain-Barré syndrome, Crohn’s disease, ulcerative colitis, psoriasis, graft-versus-host disease, systemic lupus erythematosus and insulin-dependent diabetes mellitus. Other specifically claimed aromatic heterocyclic compounds include the following:



Compound	R1	R2	Formula
292898	1-oxido-4-thiomorpholinyl	4-Me-Ph	C ₃₁ H ₃₇ N ₅ O ₃ S
292899	4-Pyr	6-Me-3-Pyr	C ₃₁ H ₃₂ N ₆ O ₂
292900	4-morpholinyl	6-MeO-3-Pyr	C ₃₀ H ₃₆ N ₆ O ₄
292901	4-morpholinyl	Me	C ₂₅ H ₃₃ N ₅ O ₃

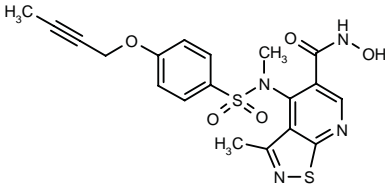
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Cirillo, P.F. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Aromatic heterocyclic cpds. as antiinflammatory agents.* WO 0043384.

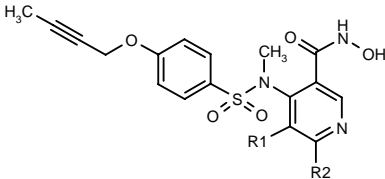
293050

4-[*N*-[4-(2-Butynyloxy)phenylsulfonyl]-*N*-methylamino]-3-methylisothiazolo[5,4-*b*]pyridine-5-carbohydroxamic acid



C19 H18 N4 O5 S2; Mol wt: 446.5062

ACTION – TNF-α-converting enzyme (TACE) inhibitor (IC₅₀ = 14 nM), potentially useful for the treatment of TNF-α-mediated disorders including osteoarthritis, rheumatoid arthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn’s disease and degenerative cartilage loss. Other specifically claimed hydroxamic acid derivatives are:



Compound	R1,R2	Formula
293051	-C(Me)=NN(Me)-	C ₂₀ H ₂₁ N ₅ O ₅ S
293052	-C(Me)=N-O-	C ₁₉ H ₁₈ N ₄ O ₆ S
293053	-CH=CHCH=C(OMe)-	C ₂₂ H ₂₁ N ₃ O ₆ S
293054	-CH=CHCH=C(Br)-	C ₂₁ H ₁₈ BrN ₃ O ₅ S

SOURCE – American Home Products.

4. de Béthune, M.-P. et al. *R165335-TMC125, a third generation nonnucleoside reverse transcriptase inhibitor (NNRTI), inhibits 97% of more than 1000 recombinant NNRTI resistant HIV clinical isolates with an IC50 below 100 nM.* AIDS 2000, 14(Suppl. 4): Abst P2.

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*Identified compound **290137** Drug Data Rep 2000, 022(09): 0823.

TREATMENT OF PROTOZOAL DISEASES

MAb R217

294144

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ACTION– Monoclonal antibody that inhibits the binding of the *Plasmodium falciparum* erythrocyte-binding protein EBA-175 to erythrocytes, as demonstrated by > 90% inhibition of the binding of [³⁵S]-methionine-labeled EBA-175 to erythrocytes. This antibody also blocked merozoite invasion in the homologous FVO (83%) and in the heterologous 3D7 (39%) strains. Potentially useful for the treatment, diagnosis and prevention of malaria. Other exemplified antibodies to EBA-175 are:

MAb R215 [294145]

MAb R256 [294146]

SOURCE – EntreMed.

REFERENCES

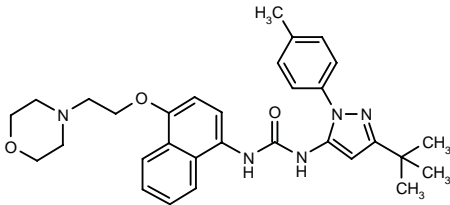
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

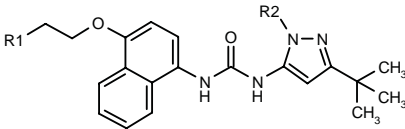
292897

N-[3-*tert*-Butyl-1-(4-methylphenyl)-1*H*-pyrazol-5-yl]-*N*'-[4-[2-(4-morpholinyl)ethoxy]naphthalen-1-yl]urea



C31 H37 N5 O3; Mol wt: 527.6653

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292899	4-Pyr	6-Me-3-Pyr	C ₃₁ H ₃₂ N ₆ O ₂
292900	4-morpholinyl	6-MeO-3-Pyr	C ₃₀ H ₃₆ N ₆ O ₄
292901	4-morpholinyl	Me	C ₂₅ H ₃₃ N ₅ O ₃

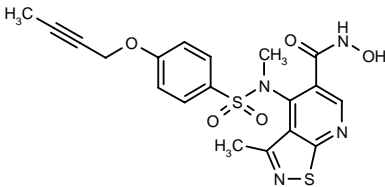
SOURCE – Boehringer Ingelheim.

REFERENCES

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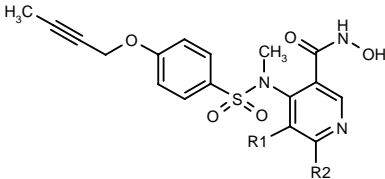
293050

4-[*N*-[4-(2-Butynyloxy)phenylsulfonyl]-*N*-methylamino]-3-methylisothiazolo[5,4-*b*]pyridine-5-carbohydroxamic acid



C19 H18 N4 O5 S2; Mol wt: 446.5062

ACTION – TNF- α -converting enzyme (TACE) inhibitor (IC₅₀ = 14 nM), potentially useful for the treatment of TNF- α -mediated disorders including osteoarthritis, rheumatoid arthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn’s disease and degenerative cartilage loss. Other specifically claimed hydroxamic acid derivatives are:



Compound	R1,R2	Formula
293051	-C(Me)=NN(Me)-	C ₂₀ H ₂₁ N ₅ O ₅ S
293052	-C(Me)=N-O-	C ₁₉ H ₁₈ N ₄ O ₆ S
293053	-CH=CHCH=C(OMe)-	C ₂₂ H ₂₁ N ₃ O ₆ S
293054	-CH=CHCH=C(Br)-	C ₂₁ H ₁₈ BrN ₃ O ₅ S

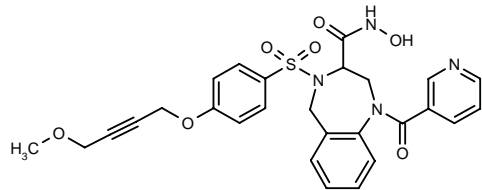
SOURCE – American Home Products.

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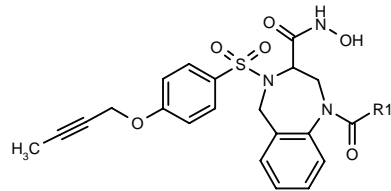
293055

4-[4-(4-Methoxy-2-butynyloxy)phenylsulfonyl]-1-(3-pyridinylcarbonyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-3-carbohydroxamic acid



C27 H26 N4 O7 S; Mol wt: 550.5894

ACTION – TNF- α -converting enzyme (TACE) inhibitor (IC_{50} = 10 nM), potentially useful for the treatment of TNF- α -mediated disorders including osteoarthritis, rheumatoid arthritis, tumor growth and degenerative cartilage loss. Other specifically claimed hydroxamic acid derivatives are:



Compound	R1	Formula
293056	Me	C ₂₂ H ₂₃ N ₃ O ₆ S
293057	2-thienyl	C ₂₅ H ₂₃ N ₃ O ₆ S ₂
293058	Ph	C ₂₇ H ₂₅ N ₃ O ₆ S
293059	CH ₂ OMe	C ₂₃ H ₂₅ N ₃ O ₇ S

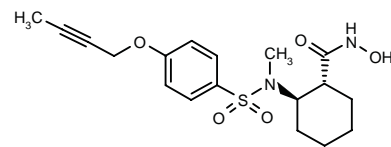
SOURCE – American Home Products.

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1. Albright, J.D. et al. (American Cyanamid Co.) *2,3,4,5-Tetrahydro-1*H*-[1,4]benzodiazepine-3-hydroxamic acid as matrix metalloproteinase inhibitors*. WO 0044730.

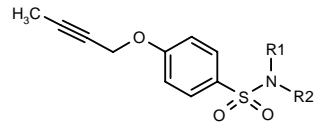
293060

(1*R*,2*R*)-2-[*N*-[4-(2-Butynyloxy)phenylsulfonyl]-*N*-methyl-amino]cyclohexanecarbohydroxamic acid



C18 H24 N2 O5 S; Mol wt: 380.4626

ACTION – TNF- α -converting enzyme (TACE) inhibitor (IC_{50} = 28 nM), potentially useful for the treatment of TNF- α -mediated disorders including osteoarthritis, rheumatoid arthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss. Other specifically claimed hydroxamic acid derivatives are:



Compound	R1	R2	Isomer	Formula
293061	2-(HONHCO)-cyclohexyl	H	1 <i>R</i> ,2 <i>R</i>	C ₁₇ H ₂₂ N ₂ O ₅ S
293062	CH ₂ CH ₂ CONHOH	H		C ₁₃ H ₁₆ N ₂ O ₅ S
293063	CH ₂ CH ₂ CONHOH	Me		C ₁₄ H ₁₈ N ₂ O ₅ S
293064	2-(HONHCO)-cyclopentyl	H	1 <i>R</i> ,2 <i>S</i>	C ₁₆ H ₂₀ N ₂ O ₅ S
293065	2-(HONHCO)-cyclopentyl	Me	1 <i>R</i> ,2 <i>S</i>	C ₁₇ H ₂₂ N ₂ O ₅ S
293066	2-(HONHCO)-cyclohexyl	H	cis	C ₁₇ H ₂₂ N ₂ O ₅ S
293067	2-(HONHCO)-cyclohexyl	Me	cis	C ₁₈ H ₂₄ N ₂ O ₅ S
293068	2-(HONHCO)-bicyclo[2.2.1]hept-3-yl	H	1 <i>R</i> ,2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i>	C ₁₈ H ₂₂ N ₂ O ₅ S
293069	2-(HONHCO)-bicyclo[2.2.1]hept-3-yl	Me	1 <i>R</i> ,2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i>	C ₁₉ H ₂₄ N ₂ O ₅ S

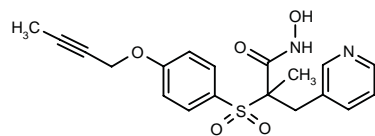
SOURCE – American Home Products.

REFERENCES

1. Levin, J.I. et al. (American Cyanamid Co.) *Acetylenic beta-sulfonamido and phosphinic acid amine hydroxamic acid TACE inhibitors*. WO 0044711.

293071

2-[4-(2-Butynyloxy)phenylsulfonyl]-2-methyl-3-(3-pyridinyl)propionohydroxamic acid



C19 H20 N2 O5 S; Mol wt: 388.4420

ACTION – A representative compound from a series of alkynyl-containing hydroxamic acids that inhibits TNF- α -converting enzyme (TACE; IC_{50} = 15.7 nM). This compound is potentially useful for the treatment of TNF- α -mediated disorders including osteoarthritis, rheumatoid arthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss.

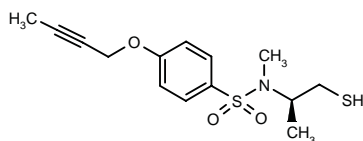
SOURCE – American Home Products.

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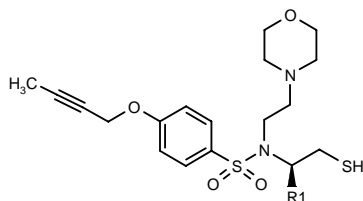
293077

4-(2-Butynyloxy)-*N*-methyl-*N*-[1(*R*)-methyl-2-sulfanyl-ethyl]benzenesulfonamide



C₁₄ H₁₉ N O₃ S₂; Mol wt: 313.4401

ACTION – TNF- α -converting enzyme (TACE) inhibitor (IC₅₀ = 273 nM), potentially useful for the treatment of TNF- α -mediated disorders including osteoarthritis, rheumatoid arthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss. Other specifically claimed acetylenic sulfonamide thiol derivatives are:



Compound	R1	Formula
293078	Me	C ₁₉ H ₂₈ N ₂ O ₄ S ₂
293080	CONH2	C ₁₉ H ₂₇ N ₃ O ₅ S ₂

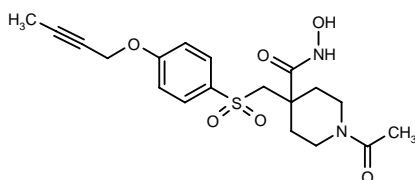
SOURCE – American Home Products.

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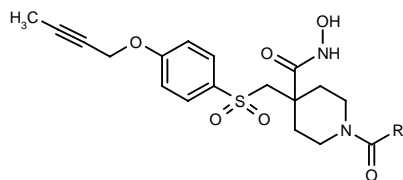
293081

1-Acetyl-4-[4-(2-butynyloxy)phenylsulfonylmethyl]-piperidine-4-carboxylic acid

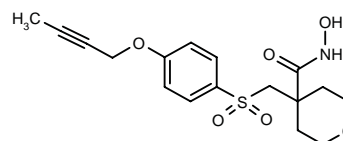


C₁₉ H₂₄ N₂ O₆ S; Mol wt: 408.4726

ACTION – TNF- α -converting enzyme (TACE) inhibitor (IC₅₀ = 4.8 nM), potentially useful for the treatment of TNF- α -mediated disorders including osteoarthritis, rheumatoid arthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss. Other specifically claimed alkynyl-containing hydroxamic acid derivatives are:



Compound	R1	Formula
293086	OMe	C ₁₉ H ₂₄ N ₂ O ₇ S
293088	2,2,5-(Me)3-1,3-dioxan-5-yl	C ₂₅ H ₃₄ N ₂ O ₈ S
293089	C(CH ₂ OH) ₂ Me	C ₂₂ H ₃₀ N ₂ O ₈ S



293083: C₁₇ H₂₁ N O₆ S

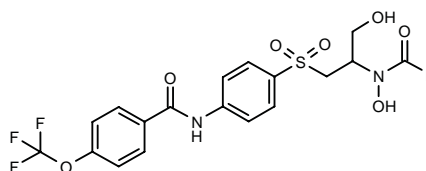
SOURCE – American Home Products.

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1. Levin, J.I. et al. (American Cyanamid Co.) *Alkynyl containing hydroxamic acid derivs., their preparation and their use as matrix metalloproteinase (MMP) inhibitors/TNF- α converting enzyme (TACE) inhibitors*. WO 0044723.

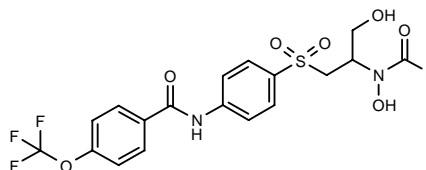
293087

N-[4-[2-(*N*-Formyl-*N*-hydroxyamino)-3-hydroxypropyl-sulfonyl]phenyl]-4-(trifluoromethoxy)benzamide

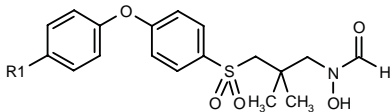


C₁₈ H₁₇ F₃ N₂ O₇ S; Mol wt: 462.3993

ACTION – Matrix metalloproteinase (MMP) inhibitor proven to inhibit MMP-2 (gelatinase A) *in vitro* with an IC₅₀ value of 0.2 nM. This compound may therefore be useful for the treatment of tissue degradation diseases including rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, corneal, epidermal or gastric ulceration, and tumor growth and metastasis. Other exemplified *N*-hydroxyformamide derivatives include the following:



Compound	R1	R2	R3	Formula
293090	H	CH ₂ OH	H	C ₁₇ H ₁₈ N ₂ O ₈ S
293091	C ₅ H ₁₁	H	CH ₂ OH	C ₂₂ H ₂₈ N ₂ O ₈ S



Compound	R1	Formula
293092	H	C ₁₈ H ₂₁ NO ₅ S
293093	OCF ₃	C ₁₉ H ₂₀ F ₃ NO ₅ S

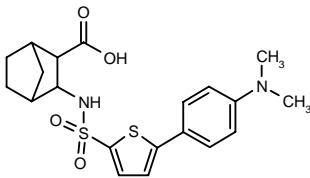
SOURCE – Abbott.

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1. Dai, Y. et al. (Abbott Laboratories Inc.) *N-Hydroxyformamide derivs. as inhibitors of matrix metalloproteinases*. WO 0044712.

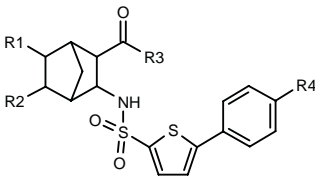
293352

3-[5-[4-(Dimethylamino)phenyl]thien-2-ylsulfonamido]-bicyclo[2.2.1]heptane-2-carboxylic acid



C20 H24 N2 O4 S2; Mol wt: 420.5516

ACTION – Matrix metalloproteinase (MMP) inhibitor with IC₅₀ values of 0.84, 0.050 and 0.38 μM against gelatinase A (MMP-2), neutrophil collagenase (MMP-8) and collagenase 3 (MMP-13), respectively. Potentially useful for the treatment of cancer, nephritis, osteoarthritis, etc. Other compounds from this series of sulfonamide derivatives having a cyclic structure include the following:



Compound	R1	R2	R3	R4	Formula
293354	bond		OH	SMe	C ₁₉ H ₁₉ NO ₄ S ₃
293355	H	H	NHOH	N(Me) ₂	C ₂₀ H ₂₅ N ₃ O ₄ S ₂

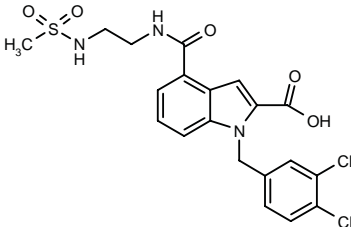
SOURCE – Shionogi.

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1. Watanabe, F. and Tsuzuki, H. (Shionogi & Co. Ltd.) *Sulfonamide derivs. having cyclic structures*. WO 0046189.

293362

1-(3,4-Dichlorobenzyl)-4-[N-[2-(methylsulfonylamido)ethyl]-carbamoyl]-1H-indole-2-carboxylic acid



C20 H19 Cl2 N3 O5 S; Mol wt: 484.3581

ACTION – Antiinflammatory agent, a monocyte chemo-attractant protein-1 (MCP-1) inhibitor (IC₅₀ = 0.64 μM against [¹²⁵I]-MCP-1 binding to human chemokine CCR2B receptors cloned in CHO cells). A representative compound from a series of indole derivatives.

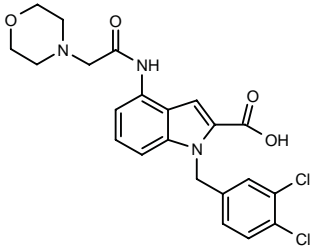
SOURCE – AstraZeneca.

REFERENCES

1. Faull, A.W. and Kettle, J. (AstraZeneca plc) *Indole derivs. and their use as MCP-1 receptor antagonists*. WO 0046197.

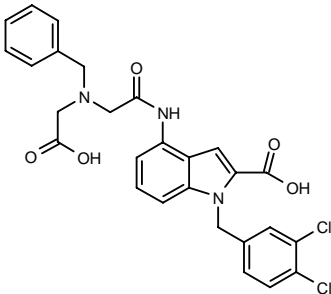
293363

1-(3,4-Dichlorobenzyl)-4-[2-(4-morpholinyl)acetamido]-1H-indole-2-carboxylic acid



C22 H21 Cl2 N3 O4; Mol wt: 462.3309

ACTION – Monocyte chemoattractant protein-1 (MCP-1) inhibitor (IC₅₀ = 1.17 μM against [¹²⁵I]-MCP-1 binding to the human MCP-1 receptor B [CCR2B] cloned in CHO cells), potentially useful for the treatment of inflammatory diseases such as rheumatoid arthritis, glomerulonephritis, pulmonary fibrosis, restenosis, etc. Another compound from this series of indole derivatives is:



293364: C27 H23 Cl2 N3 O5

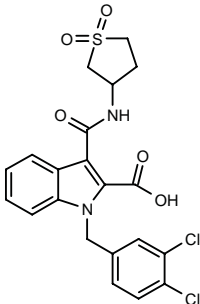
SOURCE – AstraZeneca.

REFERENCES

1. Faull, A.W. and Kettle, J. (AstraZeneca plc) *Anti-inflammatory indole derivs.* WO 0046195.

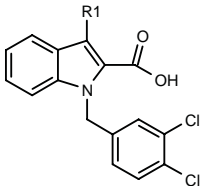
293365

1-(3,4-Dichlorobenzyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-1*H*-indole-2-carboxylic acid



C21 H18 Cl2 N2 O5 S; Mol wt: 481.3542

ACTION – Antiinflammatory agent, a monocyte chemo-attractant protein-1 (MCP-1) inhibitor (IC₅₀ = 6.86 μM against [¹²⁵I]-MCP-1 binding to human MCP-1 receptor B [CCR2B] cloned in CHO cells). Other compounds from this series of indole derivatives include the following:



Compound	R1	Formula
293366	NHCOCH2CO2H	C ₁₉ H ₁₄ Cl ₂ N ₂ O ₅
293367	OCH2CH2OH	C ₁₈ H ₁₅ Cl ₂ NO ₄

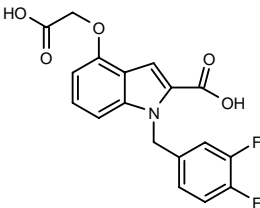
SOURCE – AstraZeneca.

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1. Faull, A.W. and Kettle, J. (AstraZeneca plc) *Chemical cpds.* WO 0046199.

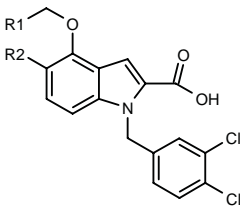
293368

4-(Carboxymethoxy)-1-(3,4-difluorobenzyl)-1*H*-indole-2-carboxylic acid



C18 H13 F2 N O5; Mol wt: 361.2987

ACTION – Antiinflammatory agent, a monocyte chemo-attractant protein-1 (MCP-1) inhibitor (IC₅₀ = 2.3 μM against [¹²⁵I]-MCP-1 binding to the human MCP-1 receptor B [CCR2B] cloned in CHO cells). Other compounds from this series of indole derivatives include the following:



Compound	R1	R2	Formula
293371	CO2H	OMe	C ₁₉ H ₁₅ Cl ₂ NO ₆
293373	CH2CH2OH	H	C ₁₉ H ₁₇ Cl ₂ NO ₄

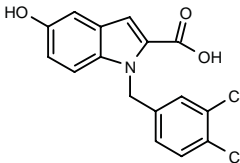
SOURCE – AstraZeneca.

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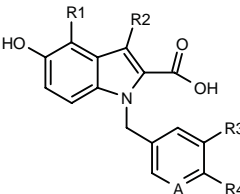
293375

1-(3,4-Dichlorobenzyl)-5-hydroxy-1*H*-indole-2-carboxylic acid



C16 H11 Cl2 N O3; Mol wt: 336.1729

ACTION – Antiinflammatory agent, a monocyte chemo-attractant protein-1 (MCP-1) inhibitor. Other compounds from this series of indole derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
293377	H	H	Cl	Cl	N	C ₁₅ H ₁₀ Cl ₂ N ₂ O ₃
293379	H	H	Cl	F	CH	C ₁₆ H ₁₁ ClFNO ₃
293380	H	H	F	Cl	CH	C ₁₆ H ₁₁ ClFNO ₃
293381	H	H	Cl	H	CH	C ₁₆ H ₁₂ ClNO ₃
293382	H	H	CF3	H	CH	C ₁₇ H ₁₂ F ₃ NO ₃
293383	H	H	H	Cl	CH	C ₁₆ H ₁₂ ClNO ₃
293385	H	Br	Cl	Cl	CH	C ₁₆ H ₁₀ BrCl ₂ NO ₃
293386	Br	H	Cl	Cl	CH	C ₁₆ H ₁₀ BrCl ₂ NO ₃
293387	H	Me	Cl	Cl	CH	C ₁₇ H ₁₃ Cl ₂ NO ₃
293389	F	H	Cl	Cl	CH	C ₁₆ H ₁₀ Cl ₂ FNO ₃
293390	H	OMe	Cl	Cl	CH	C ₁₇ H ₁₃ Cl ₂ NO ₄
293391	H	Cl	Cl	Cl	CH	C ₁₆ H ₁₀ Cl ₃ NO ₃
293392	Cl	H	Cl	Cl	CH	C ₁₆ H ₁₀ Cl ₃ NO ₃

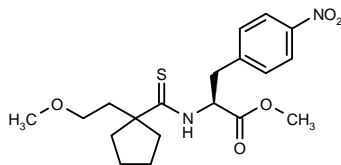
SOURCE – AstraZeneca.

REFERENCES

1. Faull, A.W. and Kettle, J.G. (AstraZeneca plc) *Indole derivs. and their use as MCP-1 antagonists*. WO 0046196.

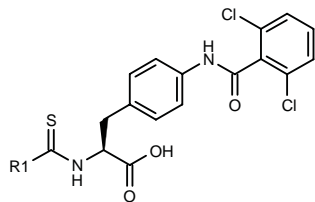
293761

N-[1-(2-Methoxyethyl)cyclopentylcarbothioyl]-4-nitro-L-phenylalanine methyl ester



C19 H26 N2 O5 S; Mol wt: 394.4894

ACTION – An inhibitor of the binding of VCAM-1 and fibronectin to VLA-4, potentially useful in the treatment of chronic inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma and inflammatory bowel disease. *In vitro*, compound gave IC₅₀ values of 4.0 and 66.5 nM, respectively, in an ELISA and a cell-based assay. Other exemplified compounds from this series of thioamide derivatives include the following:



Compound	R1	Formula
293763	1-(AcNHCH2CH2)-1-cyclopentyl	C ₂₆ H ₂₉ Cl ₂ N ₃ O ₄ S
293764	2-Cl-6-Me-Ph	C ₂₄ H ₁₉ Cl ₃ N ₂ O ₃ S
293765	1-[MeSO2(CH2)4]-1-cyclobutyl	C ₂₆ H ₃₀ Cl ₂ N ₂ O ₅ S ₂

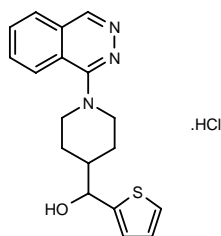
SOURCE – Roche.

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1. Hull, K.G. et al. (F. Hoffmann-La Roche AG) *Thioamide derivs*. WO 0048994.

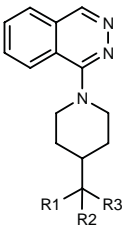
293965

1-[1-(1-Phthalazinyl)piperidin-4-yl]-1-(2-thienyl)methanol hydrochloride



C18 H19 N3 O S . HCl; Mol wt: 361.8950

ACTION – An inhibitor of the production of TNF (IC₅₀ = 5 μM in lipopolysaccharide-stimulated murine macrophages), potentially useful in the treatment of a wide range of conditions involving excessive or unregulated TNF production such as cachexia, septic shock, multiple organ failure, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, systemic lupus erythematosus, AIDS, malaria, hepatitis and type 2 diabetes. Other compounds from this series of phthalazine derivatives include the following:



Compound	R1	R2	R3	Formula
293966	H	H	Ph	C ₂₀ H ₂₁ N ₃
293967	-O-		4-MeO-Ph	C ₂₁ H ₂₁ N ₃ O ₂
293968	-O-		2-thienyl	C ₁₈ H ₁₇ N ₃ OS
293969	H	H	2-thienyl	C ₁₈ H ₁₉ N ₃ S
293970	-CH2-		Ph	C ₂₁ H ₂₁ N ₃

SOURCE – Sumitomo Pharmaceuticals.

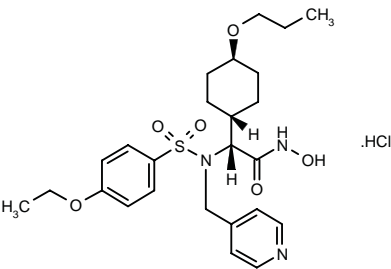
REFERENCES

1. Fujita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *TNF production inhibitors*. JP 2000191659.

CGS-33090A*

253806

2(*R*)-[4-Ethoxy-*N*-(4-pyridylmethyl)phenylsulfonamido]-2-(*trans*-4-propoxycyclohexyl)acetohydroxamic acid hydrochloride



C25 H35 N3 O6 S . HCl; Mol wt: 542.0934

ACTION – Potent, orally active dual inhibitor of matrix metalloproteinases (MMPs) and TNF-α release, suitable for use in rheumatoid arthritis. Compound exhibited broad-spectrum inhibitory activity against MMPs including stromelysin, collagenase 1, collagenase 13 and gelatinase B (IC₅₀ = 10, 61, 4 and 11 nM, respectively) and TNF-α-converting enzyme (TACE)-like activity in THP cells (IC₅₀ = 2.2 μM). *In vivo*, it inhibited the release of keratan sulfate and sulfated glycosaminoglycans into synovial fluid after intraarticular injection of stromelysin in rabbit knee joints by 86 and 80%, respectively, at a dose of 75 μmol/kg p.o. 4 h prior to challenge, and it suppressed the production of TNF-α induced by injection of lipopolysaccharide in rat joints (55% reduction at 27.5 mg/kg p.o. 4 h before challenge).

SOURCE – Novartis.

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1. Parker, D.T. (Novartis AG) *α -Substd. arylsulphonamido hydroxamic acids as TNF- α and matrix metalloproteinase inhibitors*. EP 0873312, JP 2000502088, US 5770624, WO 9722587.

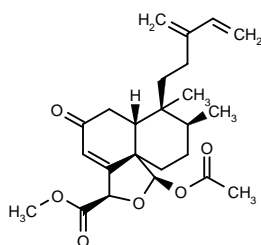
2. Parker, D. et al. *Discovery of CGS 33090A: A potent and orally active dual inhibitor of matrix metalloproteinases (MMPs) and tumor necrosis factor (TNF) α release*. Inflamm Res 2000, 49(Suppl. 2): S99.

*Identified compound **253806** (see **253481**) Drug Data Rep 1997, 019(09): 0834.

ESCULENTIN A

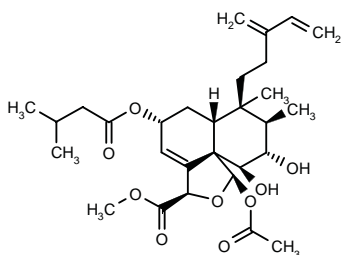
293307

(1*R*,3*R*,6*aR*,7*S*,8*S*,10*aS*)-1-Acetoxy-7,8-dimethyl-7-(3-methylene-4-pentenyl)-5-oxo-3,5,6,6*a*,7,8,9,10-octahydronaphtho[1,8*a-c*]furan-3-carboxylic acid methyl ester



C24 H32 O6; Mol wt: 416.5108

ACTION – Antiinflammatory and antineoplastic agent isolated from an extract of the plant *Caesaria esculenta*, proven to inhibit IL-1 α and TNF- α production in lipopolysaccharide-stimulated human mononuclear cells and to exert cytotoxicity against HeLa and Vero cell lines. Another compound isolated from the same source is:



Esculentin B [293309]: C29 H42 O9

SOURCE – Aventis Pharma.

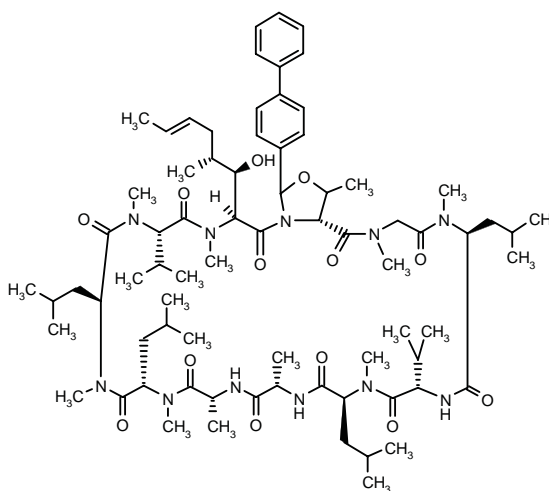
REFERENCES

1. Bal-Tembe, S. et al. (Aventis Pharma Deutschland GmbH) *Esculentin A and esculentin B, a process for their preparation, and their use in the manufacture of medicaments*. US 6107335.

IMMUNOMODULATING AGENTS

293158

(6*S*,9*S*,12*S*,15*S*,18*R*,21*S*,24*S*,27*S*,30*S*,35*aR*)-3-(Biphenyl-4-yl)-6-[1(*R*)-hydroxy-2(*R*)-methyl-4(*E*)-hexenyl]-12,15,24,30-tetraisobutyl-9,27-diisopropyl-1,7,10,13,16,18,21,25,31,34-decamethylcosahydro-1*H*-[1,3]oxazolo[3,4-*a*][1,4,7,10,13,16,19,22,25,28,31]-undecaazacyclotritriacontine-5,8,11,14,17,20,23,26,29,32,35(35*aH*)-undecaone



C75 H119 N11 O13; Mol wt: 1382.8290

ACTION – A representative compound from a series of ciclosporin derivatives whose peptide chain contains at least one pseudoproline-type non-natural amino acid radical, reported to be useful as ciclosporin prodrugs with an improved pharmacokinetic profile by virtue of their increased hydrophilic character. *In vitro*, compound inhibited cyclophilin A from bovine thymus with an IC₅₀ value 5.8-fold that of ciclosporin.

SOURCE – Debiopharm.

REFERENCES

1. Mutter, M. et al. (Debiopharm SA) *Cyclosporin derivs. and method for the production of said derivs*. WO 0046239.

SOURCE – Novartis.

REFERENCES

1. Parker, D.T. (Novartis AG) *α -Substd. arylsulphonamido hydroxamic acids as TNF- α and matrix metalloproteinase inhibitors*. EP 0873312, JP 2000502088, US 5770624, WO 9722587.

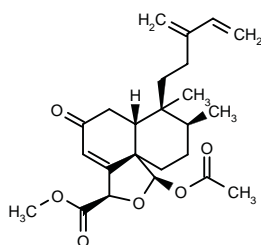
2. Parker, D. et al. *Discovery of CGS 33090A: A potent and orally active dual inhibitor of matrix metalloproteinases (MMPs) and tumor necrosis factor (TNF) α release*. Inflamm Res 2000, 49(Suppl. 2): S99.

*Identified compound **253806** (see **253481**) Drug Data Rep 1997, 019(09): 0834.

ESCULENTIN A

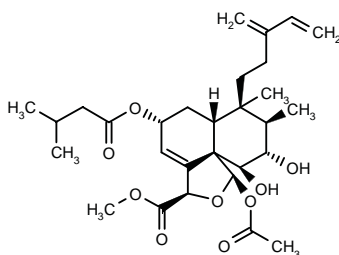
293307

(1*R*,3*R*,6*aR*,7*S*,8*S*,10*aS*)-1-Acetoxy-7,8-dimethyl-7-(3-methylene-4-pentenyl)-5-oxo-3,5,6,6*a*,7,8,9,10-octahydronaphtho[1,8*a-c*]furan-3-carboxylic acid methyl ester



C24 H32 O6; Mol wt: 416.5108

ACTION – Antiinflammatory and antineoplastic agent isolated from an extract of the plant *Caesaria esculenta*, proven to inhibit IL-1 α and TNF- α production in lipopolysaccharide-stimulated human mononuclear cells and to exert cytotoxicity against HeLa and Vero cell lines. Another compound isolated from the same source is:



Esculentin B [293309]: C29 H42 O9

SOURCE – Aventis Pharma.

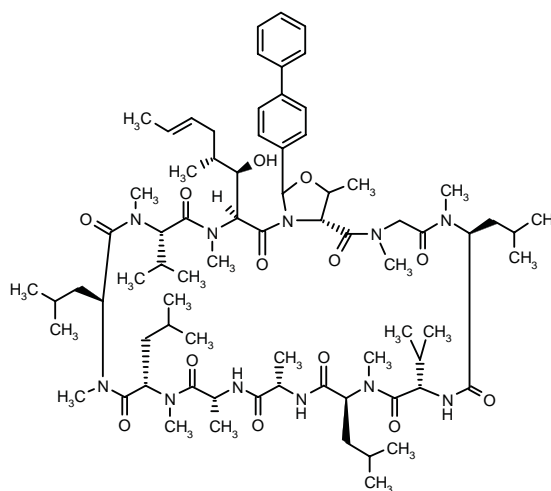
REFERENCES

1. Bal-Tembe, S. et al. (Aventis Pharma Deutschland GmbH) *Esculentin A and esculentin B, a process for their preparation, and their use in the manufacture of medicaments*. US 6107335.

IMMUNOMODULATING AGENTS

293158

(6*S*,9*S*,12*S*,15*S*,18*R*,21*S*,24*S*,27*S*,30*S*,35*aR*)-3-(Biphenyl-4-yl)-6-[1(*R*)-hydroxy-2(*R*)-methyl-4(*E*)-hexenyl]-12,15,24,30-tetraisobutyl-9,27-diisopropyl-1,7,10,13,16,18,21,25,31,34-decamethylcosahydro-1*H*-[1,3]oxazolo[3,4-*a*][1,4,7,10,13,16,19,22,25,28,31]-undecaazacyclotritriacontine-5,8,11,14,17,20,23,26,29,32,35(35*aH*)-undecaone



C75 H119 N11 O13; Mol wt: 1382.8290

ACTION – A representative compound from a series of ciclosporin derivatives whose peptide chain contains at least one pseudoproline-type non-natural amino acid radical, reported to be useful as ciclosporin prodrugs with an improved pharmacokinetic profile by virtue of their increased hydrophilic character. *In vitro*, compound inhibited cyclophilin A from bovine thymus with an IC₅₀ value 5.8-fold that of ciclosporin.

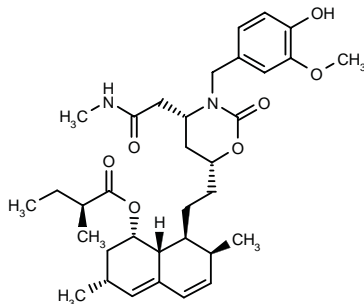
SOURCE – Debiopharm.

REFERENCES

1. Mutter, M. et al. (Debiopharm SA) *Cyclosporin derivs. and method for the production of said derivs*. WO 0046239.

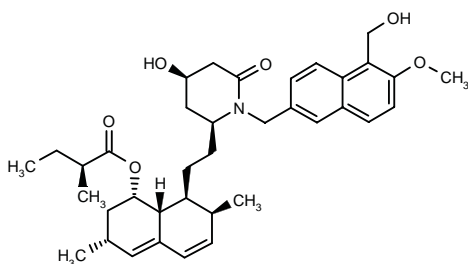
293870

2(S)-Methylbutyric acid (1*S*,3*R*,7*S*,8*S*,8*aR*)-8-[2-[3-(4-hydroxy-3-methoxybenzyl)-4(*R*)-(N-methylcarbamoylmethyl)-2-oxotetrahydro-2*H*-1,3-oxazin-6(*R*)-yl]-ethyl]-3,7-dimethyl-1,2,3,7,8,8*a*-hexahydronaphthalen-1-yl ester



C34 H48 N2 O7; Mol wt: 596.7602

ACTION – An inhibitor of LFA-1/ICAM-1 or ICAM-3 interactions with potential for the treatment of ischemia-reperfusion disorders, transplant rejection, septic shock, acute or chronic inflammatory and autoimmune diseases, skin disorders, inflammatory bowel disease and ocular disorders. *In vitro*, compound inhibited the adhesion of human LFA-1 to human ICAM-1 ($IC_{50} = 0.05 \mu M$), as well as the human mixed lymphocyte reaction (MLR; $IC_{50} = 0.2 \mu M$). *In vivo*, it inhibited thioglycolate-induced migration of neutrophils into the peritoneal cavity of mice with an ED_{50} value of $0.1 \mu g/kg$ p.o. and was active in a murine model of allergic contact dermatitis, producing 41% inhibition of oxazolone-induced ear swelling when given to sensitized mice at a dose of $3 mg/kg$ p.o. 2 h and immediately before challenge. Another specifically claimed compound from this series of mevinolin derivatives is:



293871: C37 H49 N O6

SOURCE – Novartis.

REFERENCES

1. Banteli, R. et al. (Novartis AG) *Mevinolin derivs.* WO 0048989.

LIPOSOMAL COMPLETE-CORE LIPOPOLYSACCHARIDE VACCINE

295082

Vaccine consisting of Ra chemotype lipopolysaccharide (LPS) isolated from four Gram-negative bacterial strains, mixed together to form a cocktail of complete-core LPS, and incorporated into multilamellar liposomes consisting of dimyristoyl phosphatidylcholine, dimyristoyl phosphatidylglycerol and cholesterol in a 4:1:4 molar ratio

Liposomal complete-core LPS vaccine

ACTION – Liposomal complete-core lipopolysaccharide (LPS) vaccine developed for prophylaxis in surgical and other high-risk hospitalized patients. The vaccine is nontoxic, nonpyrogenic and immunogenic against a variety of pathogens found in clinical settings including *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Bacteroides fragilis* and *Bacteroides vulgatus*. Mice actively immunized with the vaccine were protected from a lethal challenge with LPS from a strain of *E. coli*.

SOURCE – Columbia University, New York, NY (US).

REFERENCES

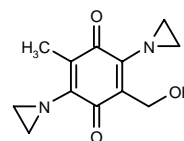
1. Bennett-Guerrero, E. et al. *Preparation and preclinical evaluation of a novel liposomal complete-core lipopolysaccharide vaccine.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 14-18, San Francisco) 2000, Abst A-508.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

RH1**295391**

2,5-Di(1-aziridiny)-3-(hydroxymethyl)-6-methyl-1,4-benzoquinone



C12 H14 N2 O3; Mol wt: 234.2536

ACTION – Antineoplastic agent, a substrate for DT-diaphorase with high cytotoxic activity against DT-diaphorase-containing cells such as human colon carcinoma HT-29 and human non-small cell lung carcinoma H460 cells ($IC_{50} = 2$ and $11 nM$, respectively). In addition, the DNA-crosslinking activity of compound, measured in primary ovarian cancer cell lines, was found to be superior to that of the clinically used anticancer agents melphalan, mitomycin C and cisplatin. In mice bearing DT-diaphorase-expressing H460 xenografts, a dose of $0.5 mg/kg$ i.p. was able to significantly delay tumor growth. Compound was rapidly eliminated from plasma after i.v. administration in mice and showed rapid metabolism in the liver; it showed reduced kidney metabolism, which contributed to its decreased systemic clearance relative to the parent compound EO9. Currently undergoing phase I/II clinical trials.

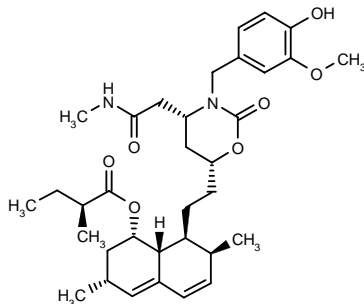
SOURCES – Cancer Research Campaign, London (GB); National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Jain, N. et al. *Analysis and stability of RH1 - A new antitumor investigative drug.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2268.

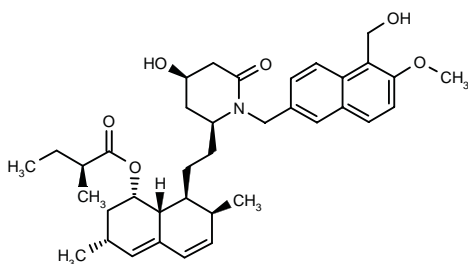
293870

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SOURCE – Columbia University, New York, NY (US).

REFERENCES

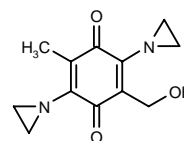
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1. Jain, N. et al. *Analysis and stability of RH1 - A new antitumor investigative drug.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2268.

2. Khan, P. et al. *Development and validation of a sensitive solid-phase extraction and high-performance liquid chromatographic assay for the novel bio-reduction anti-tumor agent RH1 in human and mouse plasma.* J Chromatogr B - Biomed Sci Appl 1999, 729(1-2): 287.

3. Loadman, P.M. et al. *Pharmacological properties of a new aziridinybenzoquinone, RH1 (2,5-diaziridiny-3-(hydroxymethyl)-6-methyl-1,4-benzoquinone), in mice.* Biochem Pharmacol 2000, 59(7): 831.

4. Ward, T.H. et al. *Crosslinking studies on the novel bioreductive anti-cancer drug RH1.* Clin Cancer Res 2000, 6(Suppl.): Abst 310.

5. Ward, T.H. et al. *Toxicity, cellular uptake and DNA crosslinking studies on the novel bioreductive anticancer drug RH1.* Br J Cancer 2000, 83(Suppl. 1): Abst P150.

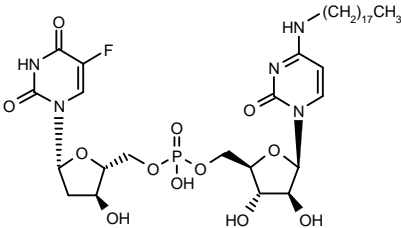
6. Winski, S.L. et al. *A new screening system for NAD(P)H: quinone oxidoreductase (NQO1)-directed antitumor quinones: Identification of a new aziridinybenzoquinone, RH1, as a NQO1-directed antitumor agent.* Clin Cancer Res 1998, 4(12): 3083.

ANTIMETABOLITES

5-FdU-NOAC

294790

Phosphoric acid (5-fluoro-2'-deoxyuridin-5'-O-yl) (*N*⁴-octadecyl-1-β-D-arabinofuranosylcytosin-5'-O-yl) diester



C36 H59 F N5 O12 P; Mol wt: 803.8571

ACTION – Potent cytotoxic agent, a new heterodinucleoside phosphate dimer composed of 5-FdU and *N*⁴-octadecyl-1-β-D-arabinofuranosylcytosine (NOAC) linked via a phosphate bond, potentially useful for the treatment of hormone-refractory prostate cancer. Compound inhibited the proliferation of human prostate carcinoma DU 145 and PC-3 cells with IC₅₀ values similar to those of 5-FdU, ranging from 3.9 μM to 5 μM. The dimer strongly inhibited thymidylate synthase following 90-min exposure, with an IC₅₀ value of 0.6 μM in both cell lines, and induced apoptosis in both DU 145 and PC-3 cells. Moreover, it induced S-phase arrest in DU 145 cells, but not PC-3 cells, in which an increase in the number of cells in the G1 phase was detected. *In vitro* experiments demonstrated that the dimer was hydrolyzed by phosphodiesterase type 1 (PDE1) and human serum to the active compounds 5-FdU and 5-FdU monophosphate. It appears to be an effective prodrug of 5-FdU and to be able to overcome 5-FdU resistance in p53-mutated and androgen-independent prostate cancer cells.

SOURCES – University Hospital, Zurich (CH); University of Tübingen, Tübingen (DE).

REFERENCES

1. Cattaneo Pangrazzi, R.M.C. et al. *The novel heterodineucleoside dimer 5-FdU-NOAC is a potent cytotoxic drug and a p53-independent inducer of apoptosis in the androgen-independent human prostate cancer cell lines PC-3 and DU-145.* Prostate 2000, 45(1): 8.

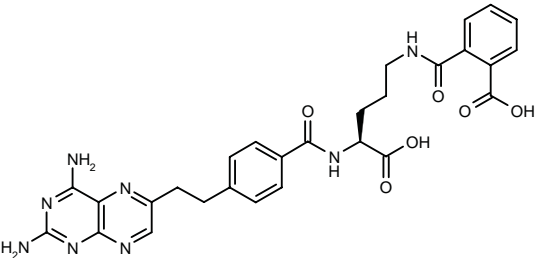
2. Cattaneo, R. et al. *Induction of cell cycle dependent cytotoxicity and apoptosis by new lipophilic heterodineucleoside phosphate dimer prodrugs of 5-fluoro-deoxyuridine and cytosine arabinoside in human cancer cells.* Clin Cancer Res 2000, 6(Suppl.): Abst 436.

PT-624*

287239

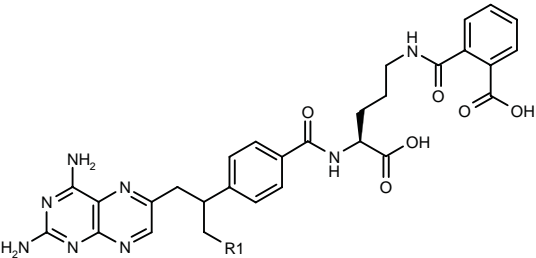
*N*²-[4-[2-(2,4-Diaminopteridin-6-yl)ethyl]benzoyl]-*N*⁵-hemipthaloyl-L-ornithine

2-[*N*-[4(*S*)-Carboxy-4-[4-[2-(2,4-diaminopteridin-6-yl)-ethyl]benzamido]butyl]carbamoyl]benzoic acid



C28 H28 N8 O6; Mol wt: 572.5792

ACTION – Antineoplastic agent with cytotoxic activity against human leukemia CCRF-CEM cells (IC₅₀ = 0.53 nM after 72-h continuous exposure) and competitive inhibitory activity against [³H]-methotrexate influx into CCRF-CEM cells via the reduced folate carrier (K_i = 0.41 μM). Other aminopterine analogues are:



Compound	R1	Formula
PT-649** [288081]	H	C ₂₉ H ₃₀ N ₈ O ₆
PT-667 [293889]	Me	C ₃₀ H ₃₂ N ₈ O ₆

SOURCES – Dana-Farber Cancer Institute, Boston, MA (US); Harvard Medical School, Boston, MA (US).

REFERENCES

1. Rosowsky, A. et al. *Analogues of the potent nonpolyglutamatable antifolate *N*^α-(4-amino-4-deoxypteroyl)-*N*^δ-hemipthaloyl-L-ornithine (PT523) with modifications in the side chain, *p*-aminobenzoyl moiety, or 9,10-bridge: Synthesis and *in vitro* antitumor activity.* J Med Chem 2000, 43(8): 1620.

2. Rosowsky, A. et al. *Efficient transport and *in vitro* cytotoxicity of 10-deaza and other analogs of *N*^α-(4-amino-4-deoxypteroyl)-*N*^δ-hemipthaloyl-L-ornithine (PT523).* Proc Amer Assoc Cancer Res 2000, 41: Abst 24.

3. Rosowsky, A. et al. *SAR analysis of the cellular influx and cytotoxicity of aminopterine analogs with a nonpolyglutamatable side chain.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PC-84.

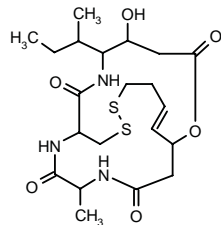
*Identified compound **287239** Drug Data Rep 2000, 022(07): 0639.

Identified compound **288081 (see **287239**) Drug Data Rep 2000, 022(07): 0639.

ANTIBIOTICS AND ALKALOIDS

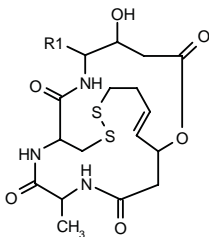
292763

5-Hydroxy-20-methyl-6-(1-methylpropyl)-2-oxa-11,12-dithia-7,19,22-triazabicyclo[7.7.6]docos-15-ene-3,8,18,21-tetrone



C21 H33 N3 O6 S2; Mol wt: 487.6387

ACTION – Depsipeptide isolated from *Pseudomonas* sp. Q71576 (FERM BP-6944) with cytotoxic activity and TGF-β-like effects in human cancer cells. Inhibition of cell proliferation was demonstrated in human colon cancer WiDr, non-small cell lung cancer A549 and prostate cancer DU 145 cells, with IC₅₀ values of 5.0 nM or less. Other exemplified compounds are:



Compound	R1	Formula
292764	i-Pr	C ₂₀ H ₃₁ N ₃ O ₆ S ₂
292765	i-Bu	C ₂₁ H ₃₃ N ₃ O ₆ S ₂

SOURCE – Yamanouchi.

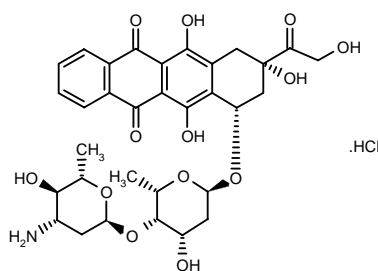
REFERENCES

1. Nagai, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel depsipeptide cpd.* WO 0042062.

MEN-11951

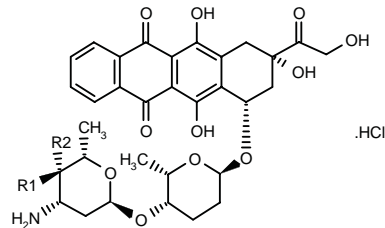
294728

7-O-[4-O-(3-Amino-2,3,6-trideoxy-α-L-mannopyranosyl)-2,6-dideoxy-α-L-galactopyranosyl]-4-demethoxyadriamycinone hydrochloride



C32 H37 N O13 . HCl; Mol wt: 680.0992

ACTION – Antitumor anthracycline that exhibits higher anticancer activity and selectivity and lower cardiotoxicity than previously known anthracyclines. It was highly cytotoxic against human non-small cell lung carcinoma H460 (IC₅₀ = 10 nM) and human small cell lung carcinoma GLC-4 cells (IC₅₀ = 11 nM). In *in vivo* studies in mice it demonstrated good efficacy against a panel of human tumor xenografts including GLC-4, H460 and human ovarian carcinoma A2780 xenografts. In addition, it was very effective against human liposarcoma SW 872, a model naturally resistant to doxorubicin treatment. Other anthracycline oligosaccharides are:



Compound	R1	R2	Formula
MEN-11860 [295877]	H	OH	C ₃₂ H ₃₇ NO ₁₂ .HCl
MEN-12265 [295884]	OH	H	C ₃₂ H ₃₇ NO ₁₂ .HCl

SOURCE – Menarini.

REFERENCES

1. Animati, F. et al. (Menarini Industrie Farma Riunite srl) *L-Arabino-disaccharides of anthracyclines, processes for their preparation, and pharmaceutical compsns. containing them.* WO 0053615.

2. Bigioni, M. et al. *Influence of sugar modification on antitumor activity in a new series of disaccharide anthracyclines.* Clin Cancer Res 2000, 6(Suppl.): Abst 325.

3. Cipollone, A. et al. *Novel anthracycline oligosaccharides: Influence of chemical modifications of the carbohydrate moiety on biological activity.* Clin Cancer Res 2000, 6(Suppl.): Abst 324.

DNA-INTERCALATING DRUGS

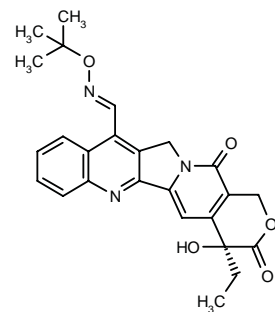
ST-1481¹⁻⁴

293886

7-(*tert*-Butoxyiminomethyl)camptothecin

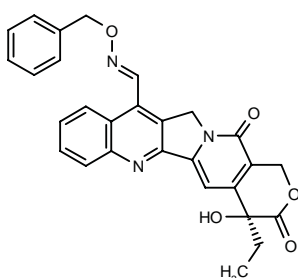
(4*S*)-4-Ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-11-carbaldehyde *O*-(*tert*-butyl)oxime

CPT-184



C25 H25 N3 O5; Mol wt: 447.4885

ACTION – Antineoplastic agent, a novel camptothecin analogue with 10-100-fold higher *in vitro* cytotoxic activity than topotecan against a panel of human carcinomas including non-small cell lung, prostate, glioma, ovarian and colon carcinomas (IC_{50} = 12-179 nM vs. 273-3537 nM for topotecan). Compound showed no crossresistance in cancer cell lines selected for resistance to clinically relevant antitumor agents such as cisplatin and doxorubicin. Its enhanced activity appears to be due to greater stabilization of the DNA–topoisomerase I complex and increased intracellular accumulation. Given orally at doses of 1-6 mg/kg, it showed strong activity against a panel of human ovarian, prostatic and lung carcinoma xenografts in nude mice, where complete tumor regressions were achieved in a large number of treated animals. Importantly, it produced complete remissions in all animals with human ovarian carcinoma A2780/Dx tumors, characterized by the multidrug resistance (MDR) phenotype, at a dose of 3 mg/kg. Selected for clinical development. Another related camptothecin derivative is:



ST-1480 [293888]:¹⁻³ C₂₈ H₂₃ N₃ O₅
CPT-172

SOURCES – Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan (IT); Sigma-Tau.

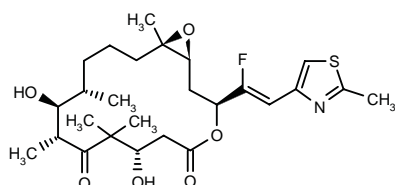
REFERENCES

1. Penco, S. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA; Istituto Nazionale per lo Studio e la Cura dei Tumori) *Camptothecin derivs. having antitumor activity*. EP 1044977, WO 0053607.
2. Dallavalle, S. et al. *Novel 7-amino- and oximinomethylene camptothecins with potent in vitro and in vivo antitumor activity*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PC-68.
3. Penco, S. et al. *Synthesis and in vitro evaluation of novel camptothecin analogs*. Clin Cancer Res 2000, 6(Suppl.): Abst 322.
4. Pisano, C. et al. *Schedule-dependent efficacy of camptothecins: Therapeutic advantages of ST1481*. Clin Cancer Res 2000, 6(Suppl.): Abst 228.

ANTIMITOTIC DRUGS

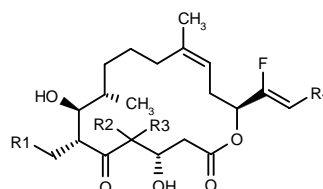
293945

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-3-[(*Z*)-1-Fluoro-2-(2-methylthiazol-4-yl)vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

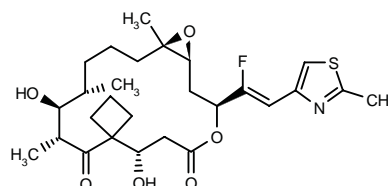


C₂₆ H₃₈ F N O₆ S; Mol wt: 511.6512

ACTION – Antineoplastic agent that interacts with tubulin by stabilizing formed microtubules. *In vitro*, compound exhibited IC_{50} values of 0.3 and 1.4 nM, respectively, against breast carcinoma MCF-7 and multidrug-resistant carcinoma NCI/ADR cells, being more potent than epothilone B (IC_{50} = 0.6 and 3.5 nM, respectively) and paclitaxel (IC_{50} = 4.0 and > 100 nM, respectively). Compound is suitable for the treatment of malignant tumors such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. In addition, it is also reported to be suited for antiangiogenesis therapy and for the treatment of chronic inflammatory diseases such as psoriasis and arthritis. Other exemplified compounds from this series of 16-halogen-epothilone derivatives include the following:



Compound	R1	R2	R3	R4	Formula
293946	H	Me	Me	2-Me-4-thiazolyl	C ₂₈ H ₃₈ FNO ₅ S
293947	H	-(CH ₂) ₃ -		2-Me-4-thiazolyl	C ₂₇ H ₃₈ FNO ₅ S
293948	Me	-(CH ₂) ₃ -		2-Me-4-thiazolyl	C ₂₈ H ₄₀ FNO ₅ S
293949	Me	Me	Me	2-Pyr	C ₂₈ H ₄₀ FNO ₅



293950: C₂₇ H₃₈ F N O₆ S

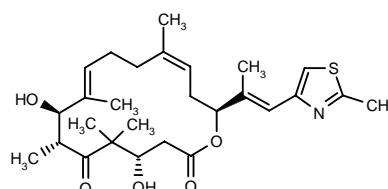
SOURCE – Schering AG.

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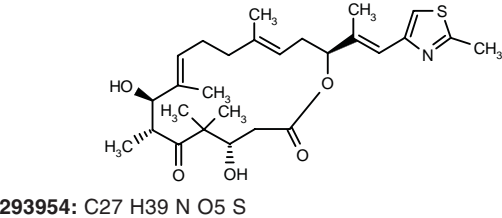
293953

(4*S*,7*R*,8*R*,16*S*)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]oxa-cyclohexadeca-9(*E*),13(*Z*)-diene-2,6-dione



C₂₇ H₃₉ N O₅ S; Mol wt: 489.6731

ACTION – Antineoplastic agent that interacts with tubulin by stabilizing formed microtubules, reported to be suitable for the treatment of malignant tumors such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. In addition, it is also reported to be suited for antiangiogenesis therapy and for the treatment of chronic inflammatory diseases such as psoriasis and arthritis. Another exemplified compound from this series of epothilone derivatives is:



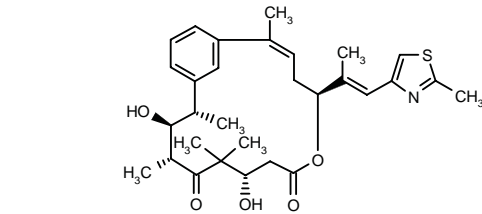
SOURCE – Schering AG.

REFERENCES

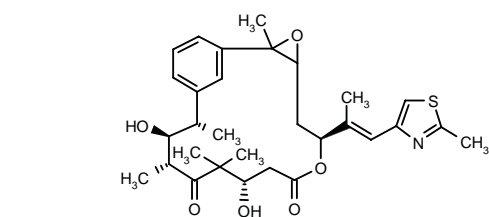
1. Klar, U. et al. (Schering AG) *Novel epothilone derivs., method for producing them and their pharmaceutical use.* DE 19908760, WO 0049019.

293955

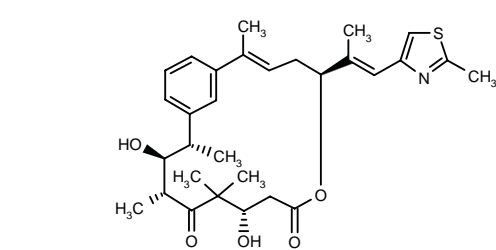
(5*S*,9*S*,12*R*,13*S*,14*S*)-9,13-Dihydroxy-2,10,10,12,14-pentamethyl-5-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]-6-oxabicyclo[13.3.1]nonadeca-1(19),2(*Z*),15,17-tetraene-7,11-dione



ACTION – Antineoplastic agent that interacts with tubulin by stabilizing formed microtubules, reported to be suitable for the treatment of malignant tumors such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. In addition, it is also reported to be suited for antiangiogenesis therapy and for the treatment of chronic inflammatory diseases such as psoriasis and arthritis. Other exemplified compounds from this series of epothilone derivatives include the following:



Compound	Isomer	Formula
293956	2 <i>R</i> ,4 <i>S</i>	C ₃₀ H ₃₉ NO ₆ S
293957	2 <i>S</i> ,4 <i>R</i>	C ₃₀ H ₃₉ NO ₆ S
293959	2 <i>S</i> ,4 <i>S</i>	C ₃₀ H ₃₉ NO ₆ S



SOURCE – Schering AG.

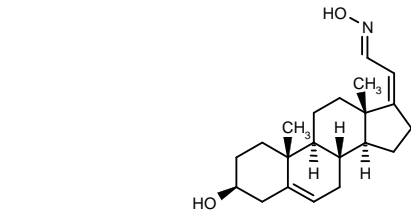
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1. Klar, U. et al. (Schering AG) *Novel epothilone derivs., method for the production thereof and their pharmaceutical application.* DE 19908763, WO 0049020.

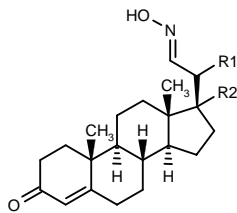
HORMONAL AGENTS

294012

(3β,17*Z*)-3-Hydroxypregna-5,17(20)-dien-21-al oxime
(17*Z*)-21-(Hydroxyimino)pregna-5,17(20)-dien-3β-ol



ACTION – Potent inhibitor of steroid 17α-hydroxylase/C₁₇₋₂₀-lyase (cytochrome P-450 17, CYP 17), giving IC₅₀ values of 0.52 and 0.077 μM against rat and human enzyme, respectively, and an IC₅₀ value of 0.23 μM against human cytochrome P-450 17 expressed in *Escherichia coli*. Compound was about 10-fold more potent than the reference ketoconazole in these assays. *In vivo*, when given to adult rats at the dose of 0.019 mmol/kg i.p. it decreased plasma testosterone levels by 57 and 44%, respectively, at 2 and 6 h after administration. A potential lead compound for further development in the treatment of prostate cancer. Other related steroidal oximes are:



Compound	R1	R2	Formula
294011	bond		C ₂₁ H ₂₉ NO ₂
294013	H	H	C ₂₁ H ₃₁ NO ₂

SOURCE – University of the Saarland, Saarbrücken (DE).

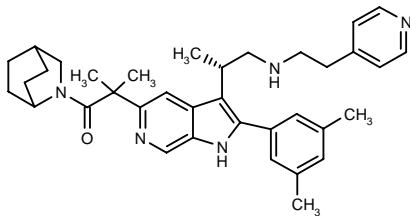
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2. Hartmann, R.W. et al. *Synthesis and evaluation of novel steroidal oxime inhibitors of P450 17 (17α-hydroxylase/C17-20-lyase)and 5α-reductase types 1 and 2.* J Med Chem 2000, 43(22): 4266.

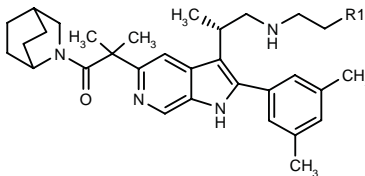
294699

1-(2-Azabicyclo[2.2.2]oct-2-yl)-2-[2-(3,5-dimethylphenyl)-3-[1(S)-methyl-2-[2-(4-pyridyl)ethylamino]ethyl]-1H-pyrrolo[2,3-c]pyridin-5-yl]-2-methylpropan-1-one



C36 H45 N5 O; Mol wt: 563.7855

ACTION – Gonadotropin-releasing hormone (GnRH or LHRH) antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as adjunctive treatment for growth hormone deficiency, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed 6-azaindole compounds are:



Compound	R1	Formula
294700	5-benzotriazolyl	C ₃₇ H ₄₈ N ₇ O
294701	2-Me-1-oxido-4-Pyr	C ₃₇ H ₄₇ N ₆ O ₂

SOURCE – Merck & Co.

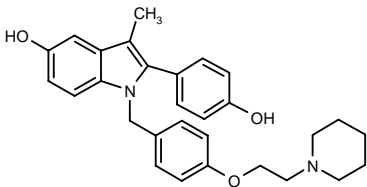
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ERA-923

272939

2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(1-piperidinyloxy)benzyl]-1H-indol-5-ol



C29 H32 N2 O3; Mol wt: 456.5828

ACTION – Selective estrogen receptor modulator (SERM) proven to inhibit estrogen binding to its receptor with an IC₅₀ of 45 nM and to exert potent antiestrogenic effects, with no agonist activity when given alone. In ER-positive human breast cancer MCF-7 cells, compound inhibited estrogen-stimulated growth (IC₅₀ = 0.7 nM) and induced cytostasis and G0/G1 cell cycle arrest. In addition, compound was active against tamoxifen- or 4-OH-tamoxifen-resistant MCF-7 cells. In tumor-bearing animals, compound (3-10 mg/kg/day p.o.) was able to inhibit estrogen-stimulated growth of tumors derived from MCF-7 (including an MCF-7 variant resistant to tamoxifen), human endometrial EnCa-101 or human ovarian BG-1 cells; in comparison, raloxifene was not active against MCF-7 or EnCa-101 xenografts. Unlike tamoxifen, compound did not induce uterotrophic effects and did not stimulate the growth of EnCa-101 tumors. In a single- and multiple-dose phase I study in healthy postmenopausal women, compound was safe and well tolerated over a wide range of doses (10-200 mg). Currently in phase II trials in women with metastatic breast cancer.

SOURCES – Ligand; Wyeth-Ayerst.

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2. Raveendranath, P. et al. (American Home Products Corp.) *Novel aryloxy-alkyl-dialkylamines.* EP 1025077, WO 9919293.

3. Gandhi, T. et al. *Safety and pharmacokinetic evaluation of ERA-923 in healthy postmenopausal women in two double masked phase I trials.* Ann Oncol 2000, 11(Suppl. 4): Abst 715P.

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6. Greenberger, L.M. et al. *Pre-clinical pharmacology profile of a new selective estrogen receptor modulator (SERM), ERA-923, for the treatment of ER positive breast cancer.* 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 166.

7. MacGregor, J.I. and Jordan, C. *Basic guide to the mechanisms of antiestrogen action.* Pharmacol Rev 1998, 50(2): 151.

8. *Product development status.* Ligand Pharmaceuticals Product Pipeline 1999.

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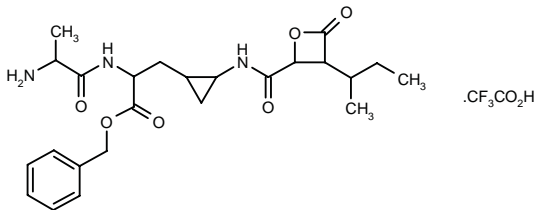
10. *Second Ligand/Wyeth-Ayerst SERM to enter clinical trials shortly.* DailyDrugNews.com (Daily Essentials) 1999, March 3.

11. *WAY-160910 designated a development candidate, triggering payment to Ligand.* DailyDrugNews.com (Daily Essentials) 2000, Jan 12.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

292912

2-(2-Aminopropionamido)-3-[2-[3-(1-methylpropyl)-4-oxo-2-oxetanylcarboxamido]cyclopropyl]propionic acid benzyl ester trifluoroacetate



C24 H33 N3 O6 . C2 H F3 O2; Mol wt: 573.5616

ACTION – A representative compound from a series of proteasome inhibitors expected to be of use for the treatment of malignant tumors, autoimmune diseases, inflammation, neurodegenerative disorders, etc. The compound inhibited proteasome activity in HeLa S3 cells (IC₅₀ = 0.03 μM) and the proliferation of human colon cancer WiDr cells (IC₅₀ = 0.05 μM). Antitumor activity was also demonstrated in nude mice bearing human colon cancer, where it produced T/C values of 56 and 49%, respectively, at 5.0 and 10.0 mg/kg i.p. for 5 days.

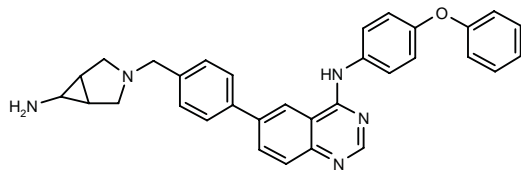
SOURCE – Kyowa Hakko.

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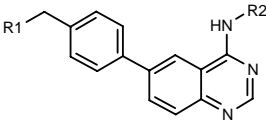
293340

N-[6-[4-(6-Amino-3-azabicyclo[3.1.0]hex-3-ylmethyl)phenyl]quinazolin-4-yl]-N-[4-(phenoxy)phenyl]amine



C32 H29 N5 O; Mol wt: 499.6151

ACTION – Agent for the treatment of cancer and other hyperproliferative disorders such as benign prostatic hypertrophy, restenosis and psoriasis that acts by inhibiting protein tyrosine kinases of the erbB family such as epidermal growth factor (EGF) receptor, erbB2, HER3 or HER4 tyrosine kinases. Within this series of hetero-aromatic bicyclic compounds, the following are also specifically claimed:



Compound	R1	R2	Formula
293342	3-azabicyclo[3.1.0]hex-6-yl-NH	4-PhO-Ph	C ₃₂ H ₂₉ N ₅ O
293343	6-(CH2OH)-3-azabicyclo[3.1.0]hex-3-yl	4-Ph-Ph	C ₃₃ H ₃₀ N ₄ O
293345	6-(CH2OH)-3-azabicyclo[3.1.0]hex-3-yl	1-(PhCH2)-5-indazolyl	C ₃₅ H ₃₂ N ₆ O
293346	3-OH-8-azabicyclo[3.2.1]oct-8-yl	4-PhO-Ph	C ₃₄ H ₃₂ N ₄ O ₂
293347	1-(CH2OH)-5-azaspiro[2.5]oct-5-yl	1-(PhSO2)-5-indolyl	C ₃₇ H ₃₅ N ₅ O ₃ S
293348	1-(CH2OH)-5-azaspiro[2.5]oct-5-yl	4-PhO-Ph	C ₃₅ H ₃₄ N ₄ O ₂

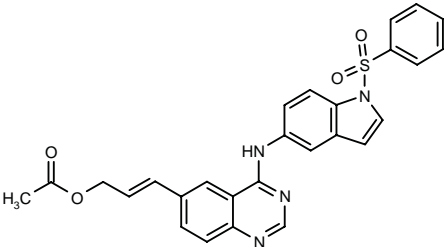
SOURCE – Pfizer.

REFERENCES

1. Kath, J.C. et al. (Pfizer Products Inc.) *Heteroaromatic bicyclic derivs. useful as anticancer agents*. EP 1029853, JP 2000309577.

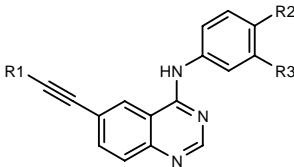
293400

Acetic acid 3-[4-[1-(phenylsulfonyl)-1H-indol-5-ylamino]-quinazolin-6-yl]-2(E)-propenyl ester



C27 H22 N4 O4 S; Mol wt: 498.5608

ACTION – Agent for the treatment of cancer and other hyperproliferative disorders such as benign prostatic hypertrophy, restenosis and psoriasis that acts by inhibiting protein tyrosine kinases of the erbB family such as epidermal growth factor (EGF) receptor, erbB2, HER3 or HER4 tyrosine kinases. Other specifically claimed substituted bicyclic compounds include the following:



Compound	R1	R2	R3	Formula
293402	3(R)-Pip	OPh	Me	C ₂₈ H ₂₆ N ₄ O
293404	CH2NHAc	OPh	Cl	C ₂₅ H ₁₉ ClN ₄ O ₂
293406	3-OH-3-Pip	F	Cl	C ₂₁ H ₁₈ ClFN ₄ O

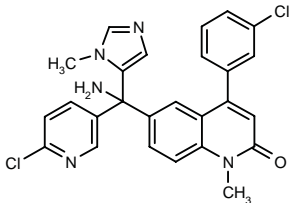
SOURCE – Pfizer.

REFERENCES

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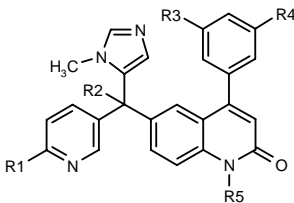
293538

6-[1-Amino-1-(6-chloropyridin-3-yl)-1-(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methylquinolin-2(1*H*)-one



C26 H21 Cl2 N5 O; Mol wt: 490.3919

ACTION – Inhibitor of abnormal cell growth that acts by inhibiting protein farnesyltransferase and Ras farnesylation. The compound is useful for the treatment of cancer and may also be effective in sensitizing abnormal cells to treatment with radiation. Other specifically claimed heteroaryl-substituted quinolin-2-one derivatives include the following:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
293541	Cl	NH2	Cl	H	cyclopropyl-CH2		C ₂₉ H ₂₅ Cl ₂ N ₅ O
293544	Cl	NH2	Cl	Cl	Me		C ₂₆ H ₂₀ Cl ₃ N ₅ O
293545	Cl	OH	OEt	H	Me		C ₂₈ H ₂₅ ClN ₄ O ₃
293546	Cl	NH2	Cl	H	H		C ₂₅ H ₁₉ Cl ₂ N ₅ O
293547	Me	NH2	Cl	H	Me		C ₂₇ H ₂₄ ClN ₅ O
293549	Cl	OH	Cl	H	cyclopropyl-CH2	(+)	C ₂₉ H ₂₄ Cl ₂ N ₄ O ₂

SOURCE – Pfizer.

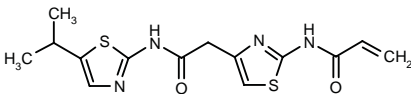
REFERENCES

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293648

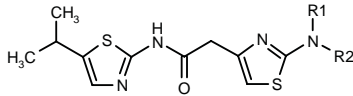
N-[4-[*N*-(5-Isopropylthiazol-2-yl)carbamoymethyl]thiazol-2-yl]acrylamide

N-(5-Isopropylthiazol-2-yl)-2-[2-(2-propenamido)thiazol-4-yl]acetamide

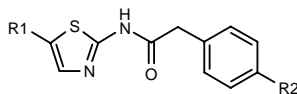


C14 H16 N4 O2 S2; Mol wt: 336.4384

ACTION – Selective inhibitor of cyclin-dependent kinases (cdk), useful for the treatment of proliferative diseases. The compound is claimed for the treatment of cancer, Alzheimer’s disease, viral infections, autoimmune diseases and neurodegenerative disorders. Other specifically claimed arylmethyl-carbonylamino-thiazoles include the following:



Compound	R1	R2	Formula
293649	H	COCH2Cl	C ₁₃ H ₁₅ ClN ₄ O ₂ S ₂
293650	H	CO(CH2)3NH2	C ₁₅ H ₂₁ N ₅ O ₂ S ₂
293651	H	1-Ac-4-Pip-CO	C ₁₉ H ₂₅ N ₅ O ₃ S ₂
293653	Me	CH2CH(OH)CH2OH	C ₁₅ H ₂₂ N ₄ O ₃ S ₂
293661	H	3-Pyr-CH2CO	C ₁₈ H ₁₉ N ₅ O ₂ S ₂



Compound	R1	R2	Formula
293655	i-Pr	1-Me-4-Piz-CH2CH2N(Me)	C ₂₂ H ₃₃ N ₅ OS
293656	i-Pr	3-Pyr-CONH	C ₂₀ H ₂₀ N ₄ O ₂ S
293659	i-Pr	NHCOC(F)2Cl	C ₁₆ H ₁₆ ClF ₂ N ₃ O ₂ S
293660	i-Pr	3-thienyl-CH2CONH	C ₂₀ H ₂₁ N ₃ O ₂ S ₂
293662	cyclopropyl	N(Me)2	C ₁₆ H ₁₉ N ₃ OS

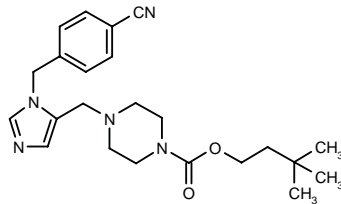
SOURCE – Pharmacia.

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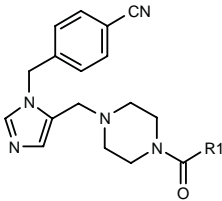
294453

4-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]piperazine-1-carboxylic acid 3,3-dimethylbutyl ester



C23 H31 N5 O2; Mol wt: 409.5309

ACTION – Inhibitor of protein prenyltransferases, particularly protein geranylgeranyltransferase type I and the prenylation of the oncogene protein Ras. Potentially useful for the treatment of cancer including but not limited to colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemia and brain tumors. The angiogenesis-inhibitory activity of this compound makes it potentially useful for the treatment of certain forms of vision deficit related to retinal vascularization. It is also indicated for the treatment of benign proliferative disorders and hepatitis delta infections, and for the prevention of restenosis and polycystic kidney disease. Other specifically claimed piperazine-containing compounds are:



Compound	R1	Formula
294454	t-BuCH2CH(OH)	C23H31N5O2
294455	t-BuCH2O	C22H29N5O2
294456	CH2CH(Et)2	C23H31N5O
294457	t-BuOCH2CH2O	C23H31N5O3
294459	t-BuCH2C(Me)2	C25H35N5O
294460	t-BuCH2CH2C(Me)2CH2O	C27H39N5O2
294462	t-BuCH(Et)O	C24H33N5O2
294464	C(Et)2Me	C23H31N5O

SOURCE – Merck & Co.

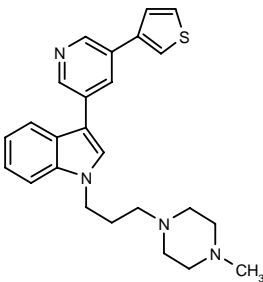
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ANGIOGENESIS INHIBITORS

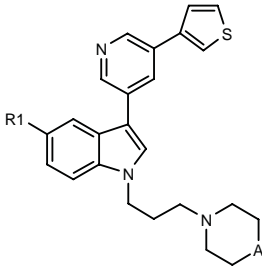
292885

1-[3-(4-Methylpiperazin-1-yl)propyl]-3-[5-(3-thienyl)pyridin-3-yl]-1*H*-indole



C25 H28 N4 S; Mol wt: 416.5902

ACTION – Angiogenesis inhibitor that acts by inhibiting tyrosine kinase enzymes, particularly vascular endothelial growth factor (VEGF) receptor kinase. The compound is expected to be useful for the treatment of cancer, retinal vascularization, diabetic retinopathy, age-related macular degeneration and inflammatory diseases including rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity. Other specifically claimed compounds are:



Compound	R1	A	Formula
292886	Cl	N(Me)	C25H27ClN4S
292887	CN	N(Me)	C26H27N5S
292888	OMe	N(Me)	C26H30N4OS
292889	H	CH2	C25H27N3S
292890	H	O	C24H25N3OS

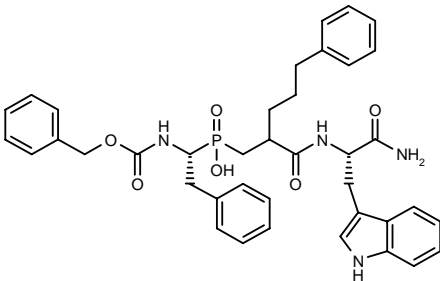
SOURCE – Merck & Co.

REFERENCES

1. Fraley, M.E. et al. (Merck & Co., Inc.) *Novel angiogenesis inhibitors*. WO 0043393.

292902

N^α-[2-[[1(*R*)-(Benzyloxycarbonylamino)-2-phenylethyl]-(hydroxy)phosphorylmethyl]-5-phenylpentanoyl]-L-tryptophanamide



C39 H43 N4 O6 P; Mol wt: 694.7647

ACTION – Phosphinic pseudopeptide inhibitor of matrix metalloproteinases (MMP) with K_i values of 54, 16, 42, 6 and 90 nM for MMP-2 (gelatinase A), MMP-8 (neutrophil collagenase), MMP-9 (gelatinase B), MMP-11 (stromelysin 3) and MMP-14 (MT-1 MMP), respectively; in contrast, the compound inhibited MMP-1 (interstitial collagenase) by 18% at 2 mM and MMP-7 (matrilysin) by 44% at 20 mM. Particularly useful for the treatment of cancer.

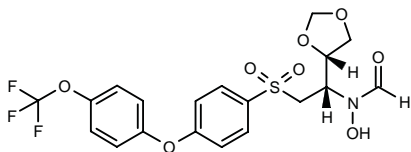
SOURCES – CNRS; INSERM, Paris Cedex (FR); Commissariat a l'Energie Atomique, Orsay Cedex (FR).

REFERENCES

1. Basset, G. et al. (Commissariat a l'Energie Atomique;INSERM [Institut National de la Sante et de la Recherche Medicale]) *Phosphinic pseudopeptides inhibitors of matrix metalloproteases*. FR 2788525, WO 0043404.

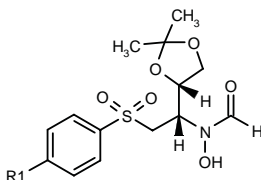
293094

N-[1(*S*)-[1,3-Dioxolan-4(*S*)-yl]-2-[4-[4-(trifluoromethoxy)-phenoxy]phenylsulfonyl]ethyl]-*N*-hydroxyformamide



C19 H18 F3 N O8 S; Mol wt: 477.4102

ACTION – Matrix metalloproteinase (MMP) inhibitor with potent activity against MMP-2 (gelatinase A) *in vitro* (IC₅₀ = 0.2 nM). Potentially useful for the treatment of tissue degradation diseases including rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, corneal, epidermal or gastric ulceration, and tumor growth and metastasis. Other exemplified hydroxamate-containing compounds are:



Compound	R1	Formula
293097	4-MeO-PhO	C ₂₁ H ₂₆ NO ₈ S
293098	4-Cl-PhO	C ₂₀ H ₂₂ ClNO ₇ S
293100	4-(MeOCH ₂ CH ₂ O)-Ph	C ₂₃ H ₂₈ NO ₈ S
293101	4-(MeOCH ₂ CH ₂ O)-PhO	C ₂₃ H ₂₈ NO ₉ S

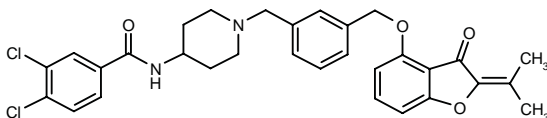
SOURCE – Abbott.

REFERENCES

1. Curtin, M.L. et al. (Abbott Laboratories Inc.) *Reverse hydroxamate inhibitors of matrix metalloproteinases*. WO 0044739.

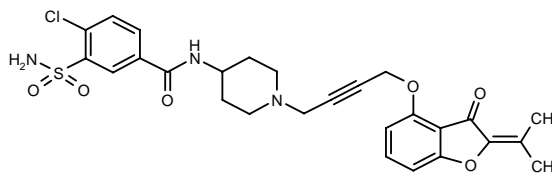
293242

3,4-Dichloro-*N*-[1-[3-(2-isopropylidene-3-oxo-2,3-dihydrobenzofuran-4-yloxymethyl)benzyl]piperidin-4-yl]benzamide



C31 H30 Cl2 N2 O4; Mol wt: 565.4940

ACTION – Antineoplastic and antimetastatic agent that displays urokinase-type plasminogen activator receptor (uPAR)-antagonist activity (IC₅₀ = 1.41 μM). Another exemplified compound from this series of *O*-substituted hydroxycoumaranone derivatives is:



293243: C27 H28 Cl N3 O6 S

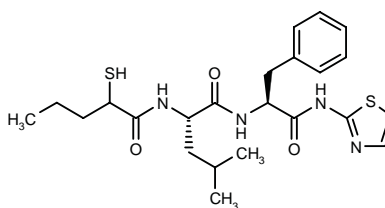
SOURCE – Roche Diagnostics.

REFERENCES

1. Friebe, W.-G. et al. (Roche Diagnostics GmbH) *O*-Substd. hydroxycoumaranone derivs. as antitumor and antimetastatic agents. EP 1026165, JP 2000226381.

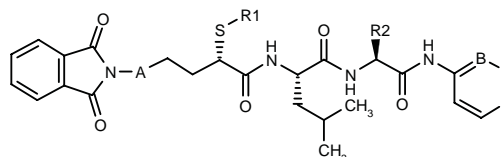
293255

N-(2-Sulfanylpentanoyl)-L-leucyl-L-phenylalanine 2-thiazolyamide



C23 H32 N4 O3 S2; Mol wt: 476.6628

ACTION – Matrix metalloproteinase (MMP) inhibitor with potential for the treatment or prevention of diseases involving tissue breakdown such as bone resorption, inflammatory diseases, dermatological conditions and tumor growth and metastasis. Other exemplified compounds include the following:



Compound	R1	R2	A	B	D	E	Formula
293261	Ac	CH2Ph	-CH2-	CH	N	CH	C ₃₅ H ₃₉ N ₅ O ₆ S
293262	H	t-Bu	-CH2-	N	CH	CH	C ₃₀ H ₃₉ N ₅ O ₅ S
293263	H	t-Bu	-(CH2)2-	N	CH	CH	C ₃₁ H ₄₁ N ₅ O ₅ S
293264	Ac	t-Bu	-CH2-	CH	CH	N	C ₃₂ H ₄₁ N ₅ O ₆ S
293265	H	t-Bu	-(CH2)2-	CH	CH	N	C ₃₁ H ₄₁ N ₅ O ₅ S

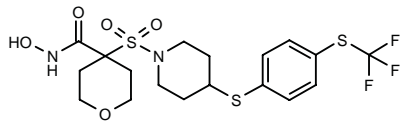
SOURCE – British Biotech.

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1. Floyd, C.D. et al. (British Biotech Pharmaceuticals Ltd.) *Metalloproteinase inhibitors*. US 6103739, WO 9703783.

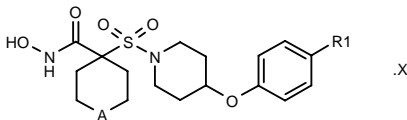
293464

4-[4-[4-(Trifluoromethylsulfanyl)phenylsulfanyl]piperidin-1-ylsulfonyl]tetrahydropyran-4-carbohydroxamic acid



C18 H23 F3 N2 O5 S3; Mol wt: 500.5807

ACTION – Matrix metalloproteinase (MMP) inhibitor, particularly active against both MMP-2 (gelatinase A; IC₅₀ < 0.1 nM) and MMP-13 (collagenase 3; IC₅₀ = 0.9 nM), while exhibiting substantially less inhibition of MMP-1 (fibroblast collagenase; IC₅₀ = 7300 nM). The compound is expected to be useful for inhibiting tumor growth and angiogenesis. Other exemplified sulfamato hydroxamates include the following:



Compound	R1	A	X	Formula
293485	CF3	-O-		C ₁₈ H ₂₃ F ₃ N ₂ O ₆ S
293486	OCF3	-N(Ph)-	HCl	C ₂₄ H ₂₈ F ₃ N ₃ O ₆ S.HCl
293487	CF3	-N(cyclopropyl)-	HCl	C ₂₁ H ₂₈ F ₃ N ₃ O ₆ S.HCl
293488	CF3	-N[C(=NH)Ph]-	HCl	C ₂₅ H ₂₉ F ₃ N ₄ O ₆ S.HCl
293489	OCF3	-N(cyclopropyl)-	HCl	C ₂₁ H ₂₈ F ₃ N ₃ O ₆ S.HCl
293491	OCF3	-N(4-Me-Ph)-		C ₂₅ H ₃₀ F ₃ N ₃ O ₆ S

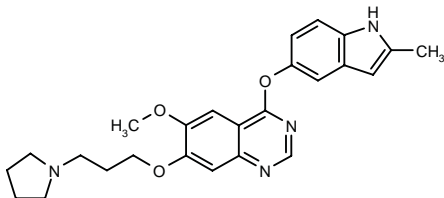
SOURCE – Pharmacia.

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1. De Crescenzo, G.A. et al. (Pharmacia Corp.) *Sulfamato hydroxamic acid metalloprotease inhibitor*. WO 0046221.

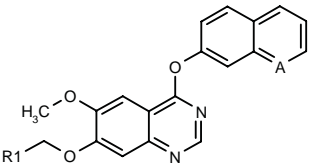
293508

6-Methoxy-4-(2-methyl-1*H*-indol-5-yloxy)-7-[3-(1-pyrrolidinyl)propoxy]quinazoline



C25 H28 N4 O3; Mol wt: 432.5212

ACTION – Vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor expected to be useful for the treatment of diseases associated with angiogenesis or increased vascular permeability. In particular, the compound is reported to inhibit the growth of primary and recurrent solid tumors associated with VEGF, especially certain tumors of the colon, breast, prostate, lung, vulva and skin. Other specifically claimed quinazoline derivatives include the following:



Compound	R1	A	Formula
293509	1-Me-4-Pip	CH	C ₂₆ H ₂₇ N ₃ O ₃
293510	4-morpholinyl-CH2CH2	N	C ₂₅ H ₂₆ N ₄ O ₄

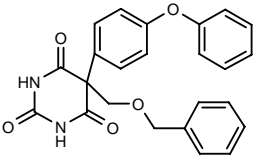
SOURCE – AstraZeneca.

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1. Hennequin, L.F.A. et al. (AstraZeneca plc;AstraZeneca SA) *Quinazoline derivs. as angiogenesis inhibitors*. WO 0047212.

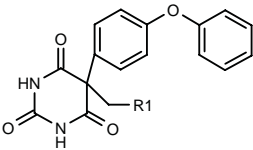
293529

5-(Benzyloxymethyl)-5-(4-phenoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione



C24 H20 N2 O5; Mol wt: 416.4310

ACTION – Matrix metalloproteinase inhibitor, particularly active against gelatinase A and B (IC₅₀ = 26 and 23 nM, respectively), potentially useful for the treatment of cancers associated with overexpression of these enzymes, especially skin, breast, prostate, colon, lung and gastric cancers. Also claimed for the treatment of diseases associated with unregulated degradation of extracellular matrix including rheumatoid arthritis, osteoarthritis, multiple sclerosis, corneal ulceration and periodontal disease. Other specifically claimed pyrimidine-2,4,6-triones are:



Compound	R1	Formula
293530	H	C ₁₇ H ₁₄ N ₂ O ₄
293531	C5H11	C ₂₂ H ₂₄ N ₂ O ₄
293533	CH2OH	C ₁₈ H ₁₆ N ₂ O ₅

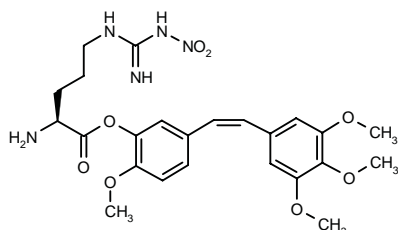
SOURCE – Roche.

REFERENCES

1. Foley, L.H. et al. (F. Hoffmann-La Roche AG) *Pyrimidine-2,4,6-triones as inhibitors of matrix metalloproteinases*. WO 0047565.

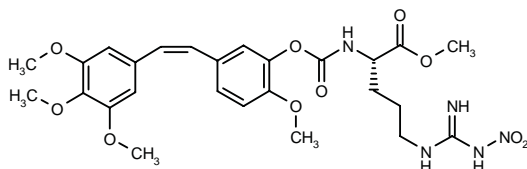
293792

N^ω-Nitro-L-arginine 2-methoxy-5-[(*Z*)-2-(3,4,5-trimethoxyphenyl)vinyl]phenyl ester



C24 H31 N5 O8; Mol wt: 517.5359

ACTION – Vascular damaging agent for the treatment of diseases involving angiogenesis, particularly solid tumors, a representative compound from a series of combretastatin derivatives bearing a moiety derived from a nitric oxide synthase inhibitor. These compounds are designed to overcome problems associated with the use of combretastatin A4 phosphate in resistant tumors, which are known to produce large amounts of NO. When tested in CaNT tumor-bearing mice, compound was found to reduce tumor functional vascular volume by 98% at 50 mg/kg i.v., with a necrosis score of 10.0 (91-100% necrosis), being more effective than combretastatin A4 phosphate (88% reduction at the same dose; necrosis score = 5.7). Another specifically claimed compound is:



293797: C26 H33 N5 O10

SOURCE – Angiogene Pharmaceuticals.

REFERENCES

1. Davis, P.D. (Angiogene Pharmaceuticals Ltd.) *Substd. stilbene cpds. with vascular damaging activity*. WO 0048590.

293883

L-Leucyl-L-seryl-L-leucyl-L-tryptophyl-L-seryl-L-glutamyl-L-tryptophyl-L-seryl-L-asparaginy-L-alanyl-L-seryl-L-valyl-L-threonyl-L-alanyl-glycinamide

C72 H106 N18 O24; Mol wt: 1607.7310

ACTION – Vascular endothelial cell migration inhibitor shown to inhibit porcine vascular endothelial cell migration by $41.5 \pm 2.1\%$ at 10 μM . Potentially useful for the treatment of diseases associated with abnormal angiogenesis including solid tumors, inflammatory diseases such as arthritis and ocular diseases such as diabetic retinopathy. Other exemplified peptides are:

L-Methionyl-L-seryl-L-glutamyl-L-tryptophyl-L-isoleucyl-L-threonyl-L-tryptophyl-L-seryl-L-prolyl-L-alanyl-L-seryl-L-isoleucyl-L-seryl-L-alanyl-glycinamide

293887: C73 H108 N18 O22 S

L-Prolyl-L-alanyl-L-prolyl-L-glutamyl-L-threonyl-L-valyl-L-glutaminy-L-arginyl-L-lysyl-L-lysyl-L-alanyl-L-arginyl-L-isoleucyl-L-arginyl-L-lysynamide

293890: C77 H141 N29 O19

SOURCE – Kyowa Hakko.

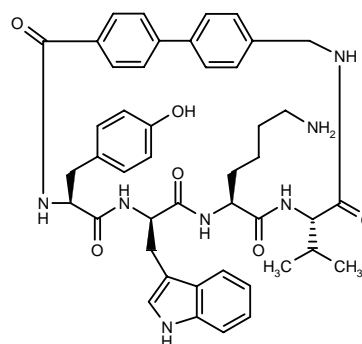
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1. Shibata, K. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Peptides inhibiting vascular endothelial cell migration*. WO 0047606.

DJS-811

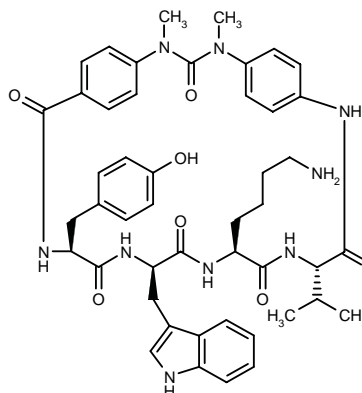
294217

(8*S*,11*R*,14*S*,17*S*)-14-(4-Aminobutyl)-8-(4-hydroxybenzyl)-11-(1*H*-indol-3-ylmethyl)-17-isopropyl-7,10,13,16,19-pentaazatricyclo[19.2.2.2^{2,5}]heptacos-1(23),2,4,21,24,26-hexaene-6,9,12,15,18-pentone



C45 H51 N7 O6; Mol wt: 785.9409

ACTION – Nonpeptide somatostatin analogue proven to selectively bind to cloned mouse sst2 and rat and human sst5 receptors ($\text{IC}_{50} = 1, 13$ and 15 nM , respectively). Compound showed superior bioavailability compared to cyclic hexapeptides and strongly inhibited angiogenesis in a mouse Matrigel model (79% inhibition at 3 mg/kg/day s.c.). Potentially useful for the treatment of cancer or for the development of imaging or radiotherapeutic agents for sst2-overexpressing tumors. Another related compound is:



DJS-631 [294215]: C47 H55 N9 O7

SOURCE – DuPont Pharmaceuticals.

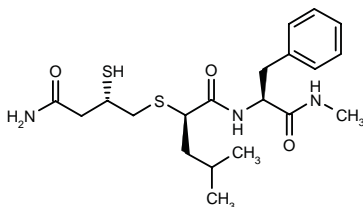
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1. Suich, D.J. et al. *Template-constrained cyclic peptide analogues of somatostatin: Subtype-selective binding to somatostatin receptors and antiangiogenic activity*. Bioorg Med Chem 2000, 8(9): 2229.

MAG-283^{1,3,4}**294792**

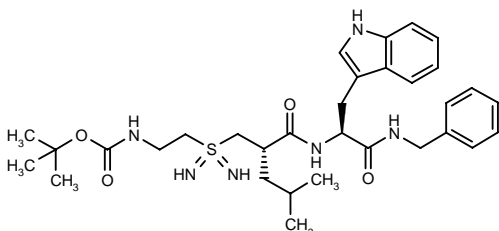
2(R)-[4-Amino-4-oxo-2(S)-sulfanylbutylsulfanyl]-N-[1(S)-benzyl-2-(methylamino)-2-oxoethyl]-4-methylpentanamide

N²-[2(R)-[4-Amino-4-oxo-2(S)-sulfanylbutylsulfanyl]-4-methylpentanoyl]-N¹-methyl-L-phenylalaninamide



C₂₀ H₃₁ N₃ O₃ S₂; Mol wt: 425.6149

ACTION – Antineoplastic agent, a matrix metalloproteinase (MMP) inhibitor with high selectivity for gelatinase A (MMP-2), gelatinase B (MMP-9) and neutrophil collagenase (MMP-8), giving respective IC₅₀ values of 3, 2.3 and 1.1 nM, over other MMPs including human interstitial collagenase (MMP-1), stromelysin (MMP-3) and matrilysin (MMP-7), with respective IC₅₀ values of 480, 280 and 14 nM. At low micromolar concentrations, it inhibited the proliferation of endothelial cells stimulated by acidic fibroblast growth factor (aFGF) and vascular endothelial growth factor (VEGF), and partially blocked cell invasion through type IV collagen. Another related MMP inhibitor is:



YLL-224 [294793]:²⁻⁴ C₃₂ H₄₆ N₆ O₄ S

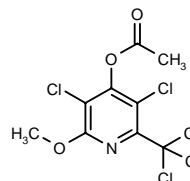
SOURCES – Aventis Pharma; Florida State University, Tallahassee, FL (US); National Institutes of Health, Bethesda, MD (US).

REFERENCES

1. Schwartz, M.A. and Wart, H.V. (Florida State University) *Mercaptosulfide metalloproteinase inhibitors*. WO 9509833.
2. Schwartz, M.A. and Wart, H.V. (Florida State University) *Sulfoximine and sulfodiimine matrix metalloproteinase inhibitors*. EP 0722321, WO 9509620.
3. Jia, M.C. et al. *Suppression of human microvascular endothelial cell invasion and morphogenesis with synthetic matrixin inhibitors. Targeting angiogenesis with MMP inhibitors*. Adv Exp Med Biol 2000, 476: 181.
4. Sang, Q.X.A. et al. *New thiol and sulfodiimine metalloproteinase inhibitors and their effect on human microvascular endothelial cell growth*. Biochem Biophys Res Commun 2000, 274(3): 780.

OTHER ONCOLYTIC DRUGS**292779**

Acetic acid 3,5-dichloro-2-methoxy-6-(trichloromethyl)pyridin-4-yl ester



C₉ H₆ Cl₅ N O₃; Mol wt: 353.4154

ACTION – Antineoplastic agent, a representative compound from a series of acyl derivatives of 4-demethylpenclomedine reported to exhibit superior activity and reduced toxicity compared to the parent compound and penclomedine. Compound displayed antitumor activity against s.c.-implanted human tumor xenografts in mice, particularly mammary MX-1 tumors, with moderate to modest activity being observed against mammary ZR-75-1 and MCF-7, CNS U-251, renal Caki-1, small cell lung NCI-H82 and colon HT-29 tumors at doses in the range of 60-90 mg/kg i.p.

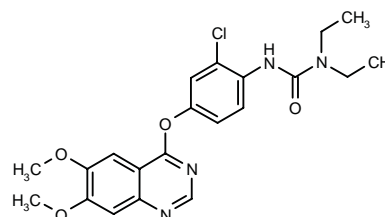
SOURCE – Southern Research Institute, Birmingham, AL (US).

REFERENCES

1. Struck, R.F. (Southern Research Institute) *Acyl derivs. of 4-demethylpenclomedine, use thereof and preparation thereof*. WO 0043010.

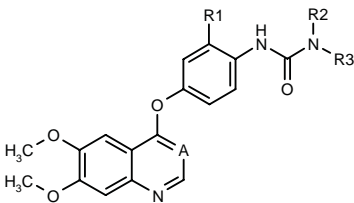
292992

N'-[2-Chloro-4-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-N,N-diethylurea



C₂₁ H₂₃ Cl N₄ O₄; Mol wt: 430.8897

ACTION – Antineoplastic agent shown to produce 83% inhibition of the growth of human glioma GL07 tumors implanted in mice at 20 mg/kg/day p.o. x 9 days. Other compounds from this series of quinoline and quinazoline derivatives include the following:



Compound	R1	R2	R3	A	Formula
292993	Cl	Et	Pr	N	C ₂₂ H ₂₅ ClN ₄ O ₄
292994	Cl	H	5-Br-2-Pyr	CH	C ₂₃ H ₁₈ BrClN ₄ O ₄
292995	NO ₂	H	2,4-(F)2-Ph	CH	C ₂₄ H ₁₈ F ₂ N ₄ O ₆

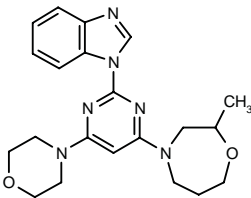
SOURCE – Kirin Brewery.

REFERENCES

1. Kubo, K. et al. (Kirin Brewery Co., Ltd.) *Quinoline derivs. and quinazoline derivs.* WO 0043366.

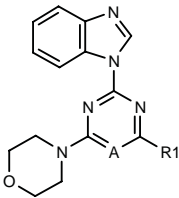
293150

1-[4-(2-Methylperhydro-1,4-oxazepin-4-yl)-6-(4-morpholinyl)pyrimidin-2-yl]-1*H*-benzimidazole



C₂₁ H₂₆ N₆ O₂; Mol wt: 394.4764

ACTION – Antineoplastic agent proven to inhibit the proliferation of human breast cancer MCF-7 cells with a GI₅₀ value of 1.1 μM. Other exemplified compounds from this series of substituted benzimidazole derivatives include the following:



Compound	R1	A	Formula
293152	2,3,6-(Me)3-4-morpholinyl	N	C ₂₁ H ₂₇ N ₇ O ₂
293153	trans-2,5-(Me)2-4-morpholinyl	N	C ₂₀ H ₂₅ N ₇ O ₂
293154	cis-2,5-(Me)2-4-morpholinyl	N	C ₂₀ H ₂₅ N ₇ O ₂
293155	2,3,5,6-(Me)4-4-morpholinyl	N	C ₂₂ H ₂₉ N ₇ O ₂
293156	2,3,6-(Me)3-4-morpholinyl	CH	C ₂₂ H ₂₈ N ₆ O ₂
293157	perhydro-1,4-oxazepin-4-yl	CH	C ₂₀ H ₂₄ N ₆ O ₂

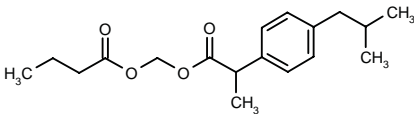
SOURCE – Zenyaku Kogyo.

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1. Kawashima, S. et al. (Zenyaku Kogyo Co., Ltd.) *Heterocyclic cpds. and antitumor agents containing the same as the active ingredient.* WO 0043385.

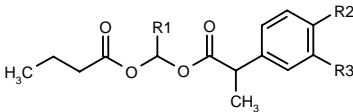
293616

Butyric acid 2-(4-isobutylphenyl)propionyloxymethyl ester



C₁₈ H₂₆ O₄; Mol wt: 306.3994

ACTION- Antineoplastic agent, a metabolically stabilized oxyalkylene ester with an acyl moiety of the carboxylic acid-containing compound ibuprofen that inhibits β-oxidation of fatty acids. The half-life for this compound was about 20.82 min. It was significantly more potent than arginine butyrate in inhibiting tumor cell clonogenicity when tested on several human neuroblastoma cell lines and exhibited at least 100-fold greater activity than arginine butyrate in inhibiting pancreatic, ovarian, breast carcinoma and melanoma cell growth. It acts by inhibiting telomerase activity and enhances tumor suppressor gene expression, especially butyric acid-responsive genes. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
293617	Me	i-Bu	H	C ₁₉ H ₂₈ O ₄
293618	Pr	i-Bu	H	C ₂₁ H ₃₂ O ₄
293619	H	-CH=C(MeO)CH=CH-		C ₁₉ H ₂₂ O ₅
293620	Me	-CH=C(MeO)CH=CH-		C ₂₀ H ₂₄ O ₅
293621	Pr	-CH=C(MeO)CH=CH-		C ₂₂ H ₂₈ O ₅

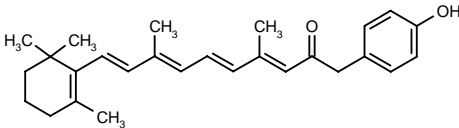
SOURCE – Beacon.

REFERENCES

1. Nudelman, A. et al. (Beacon Laboratories) *Metabolically stabilized oxyalkylene esters and uses thereof.* US 6110955.

293689

1-(4-Hydroxyphenyl)-4,8-dimethyl-10-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3(*E*),5(*E*),7(*E*),9(*E*)-decatetraen-2-one



C₂₇ H₃₄ O₂; Mol wt: 390.5636

ACTION – Antineoplastic agent for the prevention and treatment of cancers such as breast cancer and neuroblastoma, as demonstrated in human breast cancer MCF-7 cells and human neuroblastoma LA1-15n cells. This compound has the advantage of being resistant to acid-catalyzed and enzymatic hydrolysis *in vivo* and binds to serum retinol-binding protein with less affinity than previously known related compounds and is therefore expected to be less likely to exhibit night blindness as a side effect.

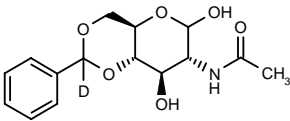
SOURCE – Ohio State University, Columbus, OH (US).

REFERENCES

1. Clagett-Dame, M. et al. (Ohio State University) *C-Linked analogs of N-(4-hydroxyphenyl) retinamide*. US 6117845.

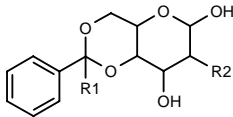
293696

2-Acetamido-4,6-*O*-(benzylidene-D₁)-2-deoxy-D-glucopyranose



C15 H18 D N O6; Mol wt: 310.3222

ACTION – Anticancer, antiviral, antibacterial and immunopotentiating agent also reported to be useful for the treatment of other disorders involving increased cell proliferation such as psoriasis, rheumatic diseases, ulcerative colitis and allergic dermatological reactions, a representative compound from a series of benzaldehyde derivatives of sugars of the hexose type. These compounds are believed to react with certain groups on the cell surface such as free amino groups to form Schiff bases, thereby altering many cellular processes such as protein synthesis, cell cycle and immune function, and are further reported to exhibit selectivity for organs or tissues having receptors with affinity for sugar moieties. *In vitro* compound was shown to induce inactivation of human cervical carcinoma NHIK-3025 and human breast carcinoma T47D cells, while *in vivo* it exhibited significant tumor growth-inhibitory activity in nude mice bearing human ovarian carcinoma SK-OV-3 or lung carcinoma A549 xenografts at 1 mg/kg/day i.v. Other exemplified compounds include the following:



Compound	R1	R2	Isomer	Formula
293699	D	OH	D-gluco	C ₁₃ H ₁₅ O ₆ D
293700	D	H	D-gluco	C ₁₃ H ₁₅ O ₅ D
293703	D	OH	D-galacto	C ₁₃ H ₁₅ O ₆ D
293704	H	OH	L-gluco	C ₁₃ H ₁₆ O ₆
293705	D	OH	L-gluco	C ₁₃ H ₁₆ O ₆

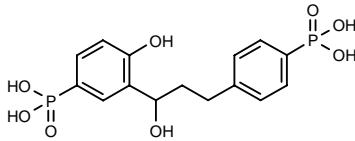
SOURCE – Norsk Hydro.

REFERENCES

1. Boerretzen, B. et al. (Norsk Hydro AS) *Chemical cpds*. WO 0048609, WO 0048610.

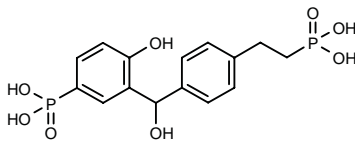
293891

4-[3-Hydroxy-3-(2-hydroxy-5-phosphonophenyl)propyl]-phenylphosphonic acid



C15 H18 O8 P2; Mol wt: 388.2472

ACTION – Adenylosuccinate synthase (AdSS) inhibitor (IC₅₀ = 30 μM for inhibition of AdSS from rabbit liver), potentially useful for the treatment of cancer including pancreatic cancer, non-small cell lung cancer, leukemia and glioma. Another exemplified compound is:



293892: C15 H18 O8 P2

SOURCE – Chugai.

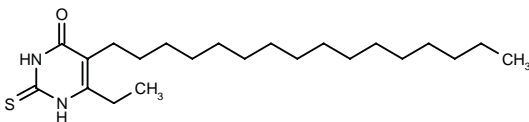
REFERENCES

1. Kobayashi, T. et al. (Chugai Pharmaceutical Co. Ltd.) *Cpds. having AdSS inhibitor effect*. JP 2000191675.

AL-6

295996

6-Ethyl-5-hexadecyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one



C22 H40 N2 O S; Mol wt: 380.6370

ACTION – Antineoplastic agent, a ceramide analogue proven to inhibit human leukemia CCRF-CEM cell proliferation (IC₅₀ = 1.7 μM) and to induce DNA fragmentation, indicative of apoptosis, after a 48-h treatment; caspase 3 was not significantly affected by compound. When given i.p. at doses ranging from 2 to 200 mg/kg for 11 days to nude mice bearing colon adenocarcinoma WiDr xenografts, it induced dose- and time-dependent reductions in tumor growth; at the dose of 20 mg/kg it exhibited comparable activity to cyclophosphamide, but at the highest dose tested it was significantly more active than cyclophosphamide, producing a 29.3% reduction in tumor mass versus a 6.4% decrease on reference drug. Compound was well tolerated in mice, with an LD₅₀ > 2000 mg/kg i.p.

SOURCES – Bracco; Università degli Studi di Pisa, Pisa (IT).

REFERENCES

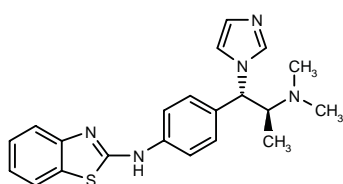
1. Fogli, S. et al. *In vitro and in vivo antitumor activity of novel ceramide analogs*. Clin Cancer Res 2000, 6(Suppl.): Abst 488.

R-116010

274501

N-[4-[2(*S*)-(Dimethylamino)-1(*S*)-(1*H*-imidazol-1-yl)prop-yl]phenyl]benzothiazol-2-amine

N-(2-Benzothiazolyl)-*N*-[4-[2(*S*)-(dimethylamino)-1(*S*)-(1*H*-imidazol-1-yl)propyl]phenyl]amine



C21 H23 N5 S; Mol wt: 377.5137

ACTION – Antineoplastic agent, a second-generation retinoic acid metabolism-blocking agent (RAMBA) that inhibits *all-trans*-retinoic acid (ATRA) metabolism in both microsomes and intact cells. Compound inhibited CYP26A in human breast cancer MCF-7 and T47D cells with respective IC₅₀s of 13 and 8.7 nM, and it was 30-100-fold more potent than liarozole fumarate; compound was also more selective as compared to liarozole fumarate for CYP26A versus other cytochrome P-450-dependent drug-metabolizing enzymes. *In vivo*, it dose-dependently inhibited the growth of androgen-independent rat prostatic adenocarcinoma R3327/PIF1 at 2.5-10 mg/kg p.o. b.i.d. for 65 days and estrogen-independent breast cancer TAH-Ha at doses of 0.08-1.25 mg/kg p.o. b.i.d. for 21 days. In another tumor model in animals inoculated with 3LL cancer cells, compound at 0.16-5 mg/kg inhibited the growth of both primary tumor and macrometastasis, with a concomitant increase in apoptosis in primary tumor cells. In all *in vivo* models, it was more effective than liarozole fumarate.

SOURCE – Janssen.

REFERENCES

1. Venet, M.G. et al. (Janssen Pharmaceutica NV) *N*-[4-(Heteroaryl)methyl]phenyl]-heteroarylamines. EP 0907650, JP 2000503670, US 6124330, WO 9749704.

2. Mabire, D. et al. *Synthesis of R116010, a retinoic acid (RA) metabolism inhibitor with antitumoral effects*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PC-60.

3. Vab Heusden, J. et al. *In vitro pharmacology of R116010, a new potent and selective inhibitor of rat RA metabolism*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3821.

4. Van Ginckel, R. et al. *Antitumoral effects of R116010, a retinoic acid metabolism inhibitor of the second generation, on experimental tumors in vivo*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2615.

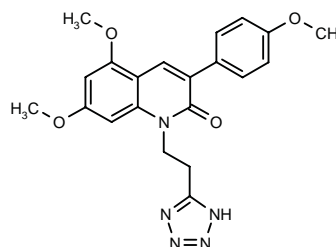
5. Van Ginckel, R. et al. *Effects of R116010, liarozole-fumarate and all-trans-retinoic acid on tumor growth and retinoic acid linked parameters*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2339.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

CRL-8256

293885

5,7-Dimethoxy-3-(4-methoxyphenyl)-1-[2-(1*H*-tetrazol-5-yl)ethyl]quinolin-2(1*H*)-one



C21 H21 N5 O4; Mol wt: 407.4279

ACTION – Noncytotoxic compound for use in cancer chemotherapy due to its ability to significantly enhance the cytotoxic antitumor activity of anticancer agents such as doxorubicin and etoposide. The effect of compound appeared to be attributable, at least in part, to inhibition of tumor cell migration.

SOURCE – Lafon.

REFERENCES

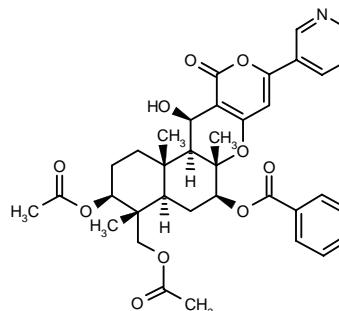
1. Joseph, B. et al. (Laboratoires L. Lafon) *Pharmaceutical compsns. comprising 2-quinolones*. FR 2781218, WO 0003990.

2. Darro, J.B. et al. *N-Substituted 3-aryl-2-quinolones: Synthesis and putative use in cancer chemotherapy*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PC-51.

PR-69

288515

(3*S*,4*R*,4*aR*,6*S*,6*aS*,12*R*,12*aS*,12*bS*)-3-Acetoxy-4-(acetoxymethyl)-6-(benzoyloxy)-12-hydroxy-4,6*a*,12*b*-trimethyl-9-(3-pyridyl)-1,3,4,4*a*,5,6,6*a*,12,12*a*,12*b*-decahydro-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one



C36 H39 N O10; Mol wt: 645.7011

ACTION – Multidrug resistance (MDR) inhibitor that is able to enhance sensitivity to doxorubicin or vincristine in resistant murine leukemia P388 cells, while displaying no cytotoxicity against drug-sensitive P388 cells. Compound was found to increase [³H]-vincristine accumulation in resistant P388 cells in a concentration- and time-dependent fashion and to inhibit P-glycoprotein. No relationship between the resistance-reversing activity of compound and its ACAT-inhibitory activity was seen and, unlike verapamil, it did not exert a Ca²⁺-antagonist effect.

SOURCE – Kitasato Institute, Tokyo (JP).

REFERENCES

1. Ohmura, S. et al. (Kitasato Institute) *Pyripyropene derivs.* JP 1996259569.

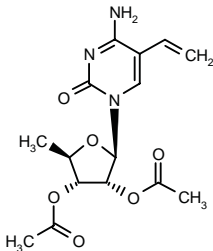
2. Fukami, A. et al. *Reversal of cancer multidrug resistance by pyripyropenes.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 1850.

3. Obata, R. et al. *Structure-activity relationships study of pyripyropenes: Reversal of cancer cell multidrug resistance.* J Antibiot 2000, 53(4): 422.

RO-09-4889

295989

2',3'-Di-O-acetyl-5'-deoxy-5-vinylcytidine



C15 H19 N3 O6; Mol wt: 337.3301

ACTION – Tumor-selective prodrug of the irreversible dihydropyrimidine dehydrogenase (DPD) inhibitor 5-vinyluracil (5-VU; IC₅₀ = 0.089 μM) that selectively generates 5-VU in tumors via the same enzymes involved in capecitabine activation, i.e., cytidine deaminase and thymidine phosphorylase. When given orally to mice bearing human cervical cancer HT-3 xenografts, it provided high levels of 5-VU in tumor tissues and intestine, but low levels in other tissues. Also in this model, combination of capecitabine and prodrug given at doses for tumor-selective DPD inhibition resulted in an increase in 5-fluorouracil (F-FU) levels, preferentially in tumors, and in an enhancement of the efficacy, but not the toxicity, of capecitabine. In contrast, title compound was not effective in enhancing capecitabine activity in tumors with very low levels of DPD activity. Potentially useful for combination therapy with fluoropyrimidines in tumors expressing high levels of DPD activity such as non-small cell lung cancer.

SOURCE – Roche.

REFERENCES

1. Hattori, K. et al. (F. Hoffmann-La Roche AG) *5'-Deoxy-cytidine derivs.* DE 19823484, EP 0882734, ES 2142763, FR 2763953, GB 2325931, JP 1998330395.

2. Hattori, K. et al. (F. Hoffmann-La Roche AG) *5'-Deoxycytidine derivs.* EP 1060183, WO 9940099.

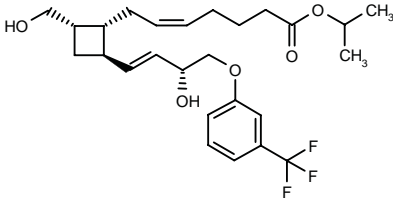
3. Miwa, M. et al. *Preclinical pharmacology of the tumor-selective DPD inhibitor RO-09-4889.* Clin Cancer Res 2000, 6(Suppl.): Abst 435.

4. Shimma, N. et al. *Design and synthesis of the tumor-selective dihydropyrimidine dehydrogenase (DPD) inhibitor RO-09-4889 for combination therapy with capecitabine.* Clin Cancer Res 2000, 6(Suppl.): Abst 434.

OCULAR MEDICATIONS

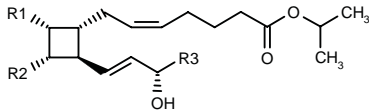
292846

7-[(1*R*,2*S*,4*S*)-2-(Hydroxymethyl)-4-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]cyclobutyl]-5(*Z*)-heptenoic acid isopropyl ester



C26 H35 F3 O5; Mol wt: 484.5515

ACTION – Ocular hypotensive agent for the treatment of glaucoma and ocular hypertension, preferably for topical administration. Other specifically claimed cyclobutane prostaglandin analogues are:



Compound	R1	R2	R3	Formula
292847	CH2OH	OH	3-CF3-PhOCH2	C ₂₆ H ₃₅ F ₃ O ₆
292848	OH	H	2-indanyl	C ₂₆ H ₃₆ O ₄
292849	CH2OH	H	2-indanyl	C ₂₇ H ₃₈ O ₄
292850	CH2OH	H	CH2CH2Ph	C ₂₆ H ₃₈ O ₄

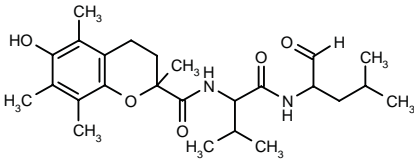
SOURCE – Alcon.

REFERENCES

1. Hellberg, M.R. (Alcon Laboratories, Inc.) *Cyclobutane prostaglandin analogues as ocular hypotensive agents.* US 6096783.

293943

N-[1-[*N*-(1-Formyl-3-methylbutyl)carbamoyl]-2-methylpropyl]-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide



C25 H38 N2 O5; Mol wt: 446.5842

ACTION – Multidrug resistance (MDR) inhibitor that is able to enhance sensitivity to doxorubicin or vincristine in resistant murine leukemia P388 cells, while displaying no cytotoxicity against drug-sensitive P388 cells. Compound was found to increase [³H]-vincristine accumulation in resistant P388 cells in a concentration- and time-dependent fashion and to inhibit P-glycoprotein. No relationship between the resistance-reversing activity of compound and its ACAT-inhibitory activity was seen and, unlike verapamil, it did not exert a Ca²⁺-antagonist effect.

SOURCE – Kitasato Institute, Tokyo (JP).

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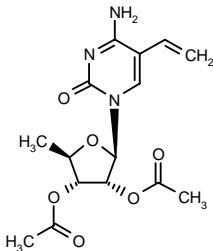
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RO-09-4889

295989

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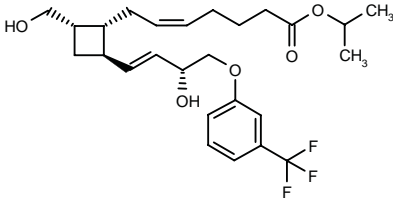
3. Miwa, M. et al. *Preclinical pharmacology of the tumor-selective DPD inhibitor RO-09-4889.* Clin Cancer Res 2000, 6(Suppl.): Abst 435.

4. Shimma, N. et al. *Design and synthesis of the tumor-selective dihydropyrimidine dehydrogenase (DPD) inhibitor RO-09-4889 for combination therapy with capecitabine.* Clin Cancer Res 2000, 6(Suppl.): Abst 434.

OCULAR MEDICATIONS

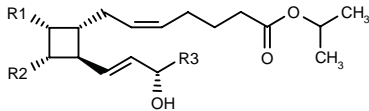
292846

7-[(1*R*,2*S*,4*S*)-2-(Hydroxymethyl)-4-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]cyclobutyl]-5(*Z*)-heptenoic acid isopropyl ester



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292849	CH2OH	H	2-indanyl	C ₂₇ H ₃₈ O ₄
292850	CH2OH	H	CH2CH2Ph	C ₂₆ H ₃₈ O ₄

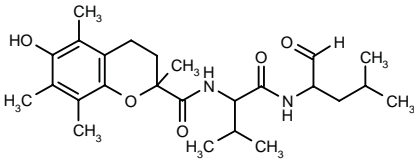
SOURCE – Alcon.

REFERENCES

1. Hellberg, M.R. (Alcon Laboratories, Inc.) *Cyclobutane prostaglandin analogues as ocular hypotensive agents.* US 6096783.

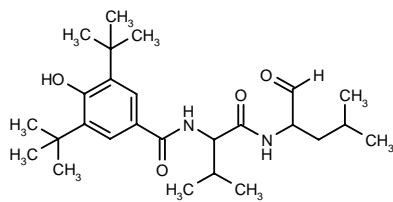
293943

N-[1-[*N*-(1-Formyl-3-methylbutyl)carbamoyl]-2-methylpropyl]-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide



C25 H38 N2 O5; Mol wt: 446.5842

ACTION – An inhibitor of calpain (IC_{50} = 0.30 μ M against μ -calpain vs. 0.21 μ M for the reference compound leupeptin), also reported to exhibit free radical-scavenging activity. Potentially useful for the treatment and prevention of cataracts, retinal disorders, macular degeneration, ocular ischemia, glaucoma and ischemia–reperfusion disorders. Another compound from this series of dipeptidylaldehyde derivatives is:



293944: C26 H42 N2 O4

SOURCE – Senju.

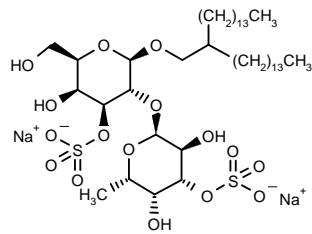
REFERENCES

1. Sakai, Y. and Inoue, J. (Senju Pharmaceuticals Co., Ltd.) *Novel dipeptidyl aldehyde derivs. and medicines containing them.* JP 2000191616.

SKK-60060

276891

2-Tetradecylhexadecyl 2-*O*-(3-*O*-sulfo-6-deoxy- α -L-galactopyranosyl)-3-*O*-sulfo- β -D-galactopyranoside disodium salt



C42 H80 Na2 O16 S2; Mol wt: 951.1900

ACTION – Selectin inhibitor that strongly binds to P- and L-selectin and inhibits their action *in vitro*. In a model of retinal ischemia–reperfusion injury in pigmented rats, compound given at a dose of 0.8 mg/kg i.v. 5 min before reperfusion induced a significant suppression of leukocyte rolling during reperfusion (67% maximal inhibition at 12 h) and reduced leukocyte accumulation (72.8% maximal inhibition at 12 h). In addition, it significantly suppressed retinal venous vasodilatation and preserved the thickness and cell density of retinal layers, especially in the inner retina.

SOURCE – Sanwa.

REFERENCES

1. Usui, T. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Sulfated and phosphated saccharide derivs., process for the preparation of the same and use thereof.* EP 0771815, JP 1997183789, US 5869460.

2. Matsubara, A. et al. *Effects of selectin inhibitor (SKK-60060) in the retinal ischemia-reperfusion model.* 24th Meet Jpn Soc Microcirc (Feb 26-27, Tokyo) 1999, Abst 1A-5.

3. Matsubara, A. et al. *Protective effects of selectin inhibitor (SKK-60060) in retinal ischemia-reperfusion injury.* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2535.

4. Matsubara, A. et al. *Protective effects of selectin ligands/inhibitor (SKK-60060) against retinal ischemia-reperfusion injury.* Exp Eye Res 2000, 71(3): 283.

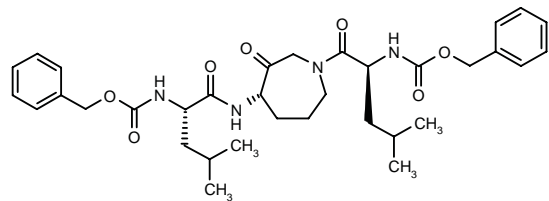
5. Yamashiro, K. et al. *Inhibitory effect of selectin inhibitor (SKK-60060) on leukocyte rolling in endotoxin-induced uveitis.* 25th Meet Jpn Soc Microcirc (Feb 18-19, Kanagawa) 2000, Abst 1A-23.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

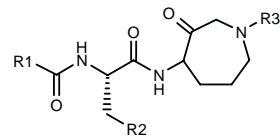
292271

*N*¹-(Benzyloxycarbonyl)-*N*²-[1-(*N*-benzyloxycarbonyl-L-leucyl)-3-oxoperhydroazepin-4(*S*)-yl]-L-leucinamide



C34 H46 N4 O7; Mol wt: 622.7584

ACTION – Cysteine and serine protease inhibitor, particularly active against cathepsin K, potentially useful in treating diseases of excessive bone loss and cartilage or matrix degradation including osteoporosis, periodontitis, gingivitis, osteoarthritis, rheumatoid arthritis, Paget’s disease, hypercalcemia of malignancy and metabolic bone disease. Other specifically claimed 4-amino-azepan-3-one derivatives include the following:



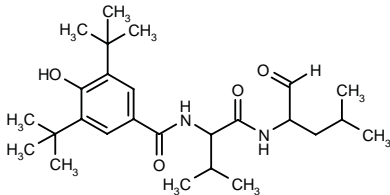
Compound	R1	R2	R3	Formula
292273	2-benzofuryl	i-Pr	3-(3-Pyr)-Ph-CH2CH2	C ₃₄ H ₃₈ N ₄ O ₄
292274	2-indolyl	i-Pr	2-Pyr-SO2	C ₂₈ H ₃₁ N ₅ O ₅ S
292275	NHCH2Ph	i-Pr	2-Pyr-SO2	C ₂₅ H ₃₃ N ₅ O ₅ S
292276	3-Me-2-benzofuryl	i-Pr	2-Pyr-SO2	C ₂₇ H ₃₂ N ₄ O ₆ S
292277	5,6-(MeO)2-2-benzofuryl	i-Pr	3-Cl-PhSO2	C ₂₉ H ₃₄ ClN ₅ O ₆ S
292278	5,6-(MeO)2-2-benzofuryl	i-Pr	3-MeO-PhSO2	C ₃₀ H ₃₇ N ₃ O ₉ S
292279	1,3-benzodioxol-5-yl	i-Pr	SO2Me	C ₂₁ H ₂₉ N ₃ O ₇ S
292280	5-(3-CF3-Ph)-2-furyl	cyclohexyl	2-Pyr-SO2	C ₃₂ H ₃₅ F ₃ N ₄ O ₆ S

SOURCE – GlaxoSmithKline.

REFERENCES

1. Marquis, R.W. Jr. et al. (SmithKline Beecham Corp.) *Protease inhibitors.* WO 0038687.

ACTION – An inhibitor of calpain (IC_{50} = 0.30 μ M against μ -calpain vs. 0.21 μ M for the reference compound leupeptin), also reported to exhibit free radical-scavenging activity. Potentially useful for the treatment and prevention of cataracts, retinal disorders, macular degeneration, ocular ischemia, glaucoma and ischemia–reperfusion disorders. Another compound from this series of dipeptidylaldehyde derivatives is:



293944: C26 H42 N2 O4

SOURCE – Senju.

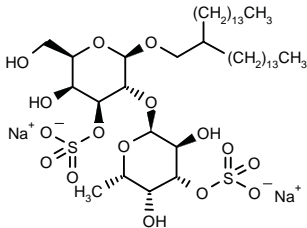
REFERENCES

1. Sakai, Y. and Inoue, J. (Senju Pharmaceuticals Co., Ltd.) *Novel dipeptidyl aldehyde derivs. and medicines containing them.* JP 2000191616.

SKK-60060

276891

2-Tetradecylhexadecyl 2-*O*-(3-*O*-sulfo-6-deoxy- α -L-galactopyranosyl)-3-*O*-sulfo- β -D-galactopyranoside disodium salt



C42 H80 Na2 O16 S2; Mol wt: 951.1900

ACTION – Selectin inhibitor that strongly binds to P- and L-selectin and inhibits their action *in vitro*. In a model of retinal ischemia–reperfusion injury in pigmented rats, compound given at a dose of 0.8 mg/kg i.v. 5 min before reperfusion induced a significant suppression of leukocyte rolling during reperfusion (67% maximal inhibition at 12 h) and reduced leukocyte accumulation (72.8% maximal inhibition at 12 h). In addition, it significantly suppressed retinal venous vasodilatation and preserved the thickness and cell density of retinal layers, especially in the inner retina.

SOURCE – Sanwa.

REFERENCES

1. Usui, T. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Sulfated and phosphated saccharide derivs., process for the preparation of the same and use thereof.* EP 0771815, JP 1997183789, US 5869460.

2. Matsubara, A. et al. *Effects of selectin inhibitor (SKK-60060) in the retinal ischemia-reperfusion model.* 24th Meet Jpn Soc Microcirc (Feb 26-27, Tokyo) 1999, Abst 1A-5.

3. Matsubara, A. et al. *Protective effects of selectin inhibitor (SKK-60060) in retinal ischemia-reperfusion injury.* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2535.

4. Matsubara, A. et al. *Protective effects of selectin ligands/inhibitor (SKK-60060) against retinal ischemia-reperfusion injury.* Exp Eye Res 2000, 71(3): 283.

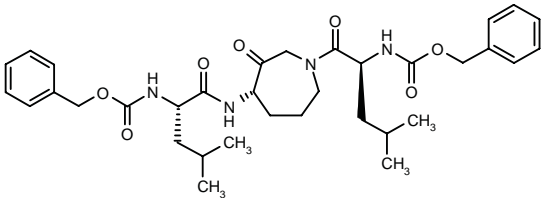
5. Yamashiro, K. et al. *Inhibitory effect of selectin inhibitor (SKK-60060) on leukocyte rolling in endotoxin-induced uveitis.* 25th Meet Jpn Soc Microcirc (Feb 18-19, Kanagawa) 2000, Abst 1A-23.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

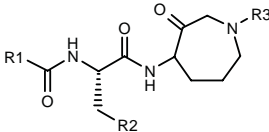
292271

*N*¹-(Benzyloxycarbonyl)-*N*²-[1-(*N*-benzyloxycarbonyl-L-leucyl)-3-oxoperhydroazepin-4(*S*)-yl]-L-leucinamide



C34 H46 N4 O7; Mol wt: 622.7584

ACTION – Cysteine and serine protease inhibitor, particularly active against cathepsin K, potentially useful in treating diseases of excessive bone loss and cartilage or matrix degradation including osteoporosis, periodontitis, gingivitis, osteoarthritis, rheumatoid arthritis, Paget’s disease, hypercalcemia of malignancy and metabolic bone disease. Other specifically claimed 4-amino-azepan-3-one derivatives include the following:



Compound	R1	R2	R3	Formula
292273	2-benzofuryl	i-Pr	3-(3-Pyr)-Ph-CH2CH2	C ₃₄ H ₃₈ N ₄ O ₄
292274	2-indolyl	i-Pr	2-Pyr-SO2	C ₂₈ H ₃₁ N ₅ O ₅ S
292275	NHCH2Ph	i-Pr	2-Pyr-SO2	C ₂₅ H ₃₃ N ₅ O ₅ S
292276	3-Me-2-benzofuryl	i-Pr	2-Pyr-SO2	C ₂₇ H ₃₂ N ₄ O ₆ S
292277	5,6-(MeO)2-2-benzofuryl	i-Pr	3-Cl-PhSO2	C ₂₉ H ₃₄ ClN ₅ O ₆ S
292278	5,6-(MeO)2-2-benzofuryl	i-Pr	3-MeO-PhSO2	C ₃₀ H ₃₇ N ₃ O ₉ S
292279	1,3-benzodioxol-5-yl	i-Pr	SO2Me	C ₂₁ H ₂₉ N ₃ O ₇ S
292280	5-(3-CF3-Ph)-2-furyl	cyclohexyl	2-Pyr-SO2	C ₃₂ H ₃₅ F ₃ N ₄ O ₆ S

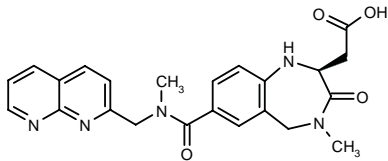
SOURCE – GlaxoSmithKline.

REFERENCES

1. Marquis, R.W. Jr. et al. (SmithKline Beecham Corp.) *Protease inhibitors.* WO 0038687.

293165

2-[4-Methyl-7-[N-methyl-N-(1,8-naphthyridin-2-ylmethyl)carbamoyl]-3-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-2(*S*)-yl]acetic acid



C23 H23 N5 O4; Mol wt: 433.4657

ACTION – α_v integrin, particularly $\alpha_v\beta_3$, $\alpha_v\beta_5$ and/or $\alpha_v\beta_6$, receptor antagonist, potentially useful for inhibiting bone resorption and for the treatment or prevention of osteoporosis, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, viral disease, and tumor growth and metastasis. A specifically claimed compound from a series of benzazepine derivatives.

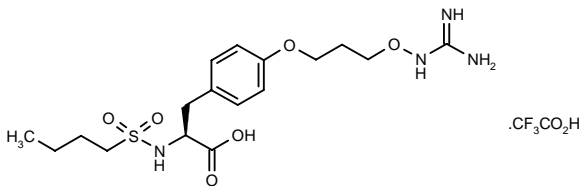
SOURCE – Merck & Co.

REFERENCES

1. Askew, B.C. (Merck & Co., Inc.) *Benzazepine derivs. as α -V integrin receptor antagonists*. WO 0046215.

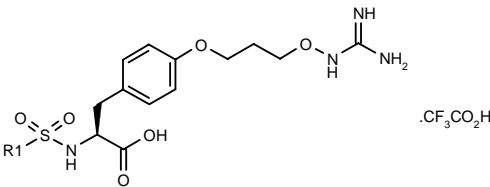
293496

N-(Butylsulfonyl)-4-*O*-(3-guanidinooxypropyl)-L-tyrosine trifluoroacetate



C17 H28 N4 O6 S . C2 H F3 O2; Mol wt: 530.5181

ACTION – Selective inhibitor of α_v integrins, particularly $\alpha_v\beta_3$ and $\alpha_v\beta_5$, as demonstrated by an IC_{50} value of 28 nM for inhibition of the vitronectin- $\alpha_v\beta_3$ interaction compared to an IC_{50} value of 780 nM for inhibition of the fibrinogen-gpIIb/IIIa interaction. Potentially useful for the treatment of tumor growth, metastasis, restenosis, osteoporosis, inflammation, macular degeneration, diabetic retinopathy and rheumatoid arthritis. Other exemplified compounds from this series of tyrosine alkoxyguanidines include the following:



Compound	R1	Formula
293497	2-Me-5-NO2-Ph	C ₂₀ H ₂₅ N ₅ O ₈ S.C ₂ HF ₃ O ₂
293498	2,6-(Cl)2-Ph	C ₁₈ H ₂₂ Cl ₂ N ₄ O ₆ S.C ₂ HF ₃ O ₂
293499	5-Cl-1,3-(Me)2-4-pyrazolyl	C ₁₈ H ₂₅ ClN ₆ O ₆ S.C ₂ HF ₃ O ₂
293500	7,7-(Me)2-2-oxo-bicyclo[2.2.1]hept-1-yl-CH2	C ₂₃ H ₃₄ N ₄ O ₇ S.C ₂ HF ₃ O ₂

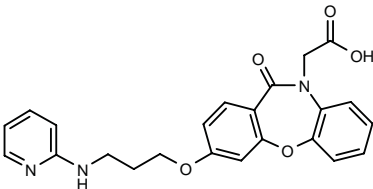
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Tomczuk, B.E. and Lee, Y.K. (3-Dimensional Pharmaceuticals, Inc.) *Tyrosine alkoxyguanidines as integrin inhibitors*. WO 0047552.

293519

2-[11-Oxo-3-[3-(2-pyridylamino)propoxy]-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-10-yl]acetic acid



C23 H21 N3 O5; Mol wt: 419.4349

ACTION – A specifically claimed compound from a series of dibenzazepine derivatives with integrin receptor-antagonist activity, particularly active at $\alpha_v\beta_3$, $\alpha_v\beta_5$ and/or $\alpha_v\beta_6$ receptors. Potentially useful for inhibiting bone resorption and treating osteoporosis, as well as for the treatment of vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, inflammation, tumor growth and metastasis.

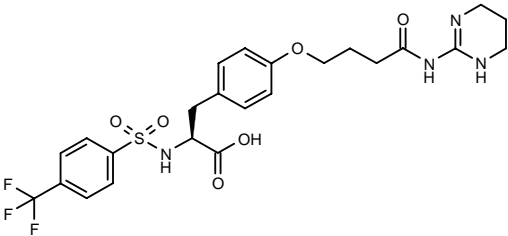
SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. and Newton, R.C. (Merck & Co., Inc.) *Dibenzo-azepine derivs. as α V integrin receptor antagonists*. WO 0048603.

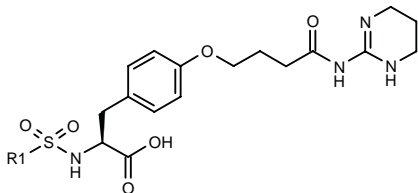
293532

4-*O*-[3-[*N*-(1,4,5,6-Tetrahydropyrimidin-2-yl)carbamoyl]-propyl]-*N*-[4-(trifluoromethyl)phenylsulfonyl]-L-tyrosine



C24 H27 F3 N4 O6 S; Mol wt: 556.5593

ACTION – Agent for the treatment or prevention of bone disorders, particularly osteoporosis, as well as cancer, inflammatory disorders, cardiovascular diseases, restenosis, arteriosclerosis, nephropathies, retinopathies and rheumatoid arthritis, a selective vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist. *In vitro*, compound inhibited kistrin binding to the human vitronectin receptor with an IC_{50} value of 3.5 nM, while exhibiting an IC_{50} value of 3150 nM for inhibition of fibrinogen binding to the gpIIb/IIIa receptor. Other exemplified compounds from this series of acylguanidine derivatives include the following:



Compound	R1	Formula
293534	1-Naph	C ₂₇ H ₃₀ N ₄ O ₆ S
293535	4-Cl-Ph	C ₂₃ H ₂₇ ClN ₄ O ₆ S
293536	Ph	C ₂₃ H ₂₈ N ₄ O ₆ S
293537	4-Me-Ph	C ₂₄ H ₃₀ N ₄ O ₆ S
293539	4-Br-Ph	C ₂₃ H ₂₇ BrN ₄ O ₆ S
293540	2-thienyl	C ₂₁ H ₂₆ N ₄ O ₆ S ₂
293542	Bu	C ₂₁ H ₃₂ N ₄ O ₆ S
293543	C8H17	C ₂₆ H ₄₀ N ₄ O ₆ S

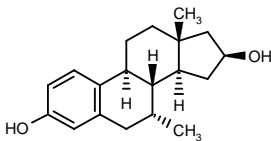
SOURCES – Aventis Pharma; Genentech.

REFERENCES

1. Peyman, A. et al. (Aventis Pharma Deutschland GmbH;Genentech, Inc.) *Novel guanidine derivs. as inhibitors of cell adhesion*. EP 1028114, WO 0047564.

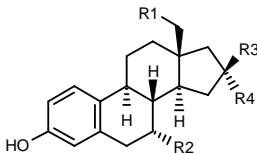
293652

7 α -Methylestra-1,3,5(10)-triene-3,16 β -diol



C19 H26 O2; Mol wt: 286.4124

ACTION – Tissue-selective estrogen with higher affinity for estrogen receptors from rat prostate than for receptors from rat uterus. *In vivo* it was more effective in protecting against hormone deficiency-associated bone loss than in stimulating the uterus. It may thus be used in hormone replacement therapy for alleviating the symptoms associated with the andropause or the menopause, and for the treatment of osteoporosis, atherosclerosis, rheumatoid arthritis, benign prostate hyperplasia, male and female infertility, among others. Other exemplified 16-hydroxyestratrienes include the following:



Compound	R1	R2	R3	R4	Formula
293654	H	Me	H	OH	C ₁₉ H ₂₆ O ₂
293657	Me	H	H	OH	C ₁₉ H ₂₆ O ₂
293658	Me	H	OH	H	C ₁₉ H ₂₆ O ₂

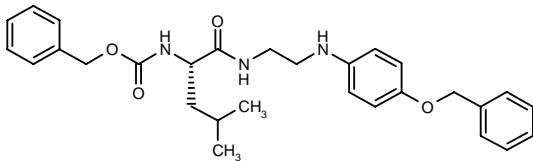
SOURCE – Schering AG.

REFERENCES

1. Künzer, H. et al. (Schering AG) *16-Hydroxyestratrienes as selective estrogens*. DE 19906159, WO 0047603.

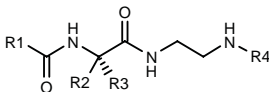
293709

*N*²-(Benzyloxycarbonyl)-*N*¹-[2-[4-(benzyloxy)phenyl-amino]ethyl]-L-leucinamide

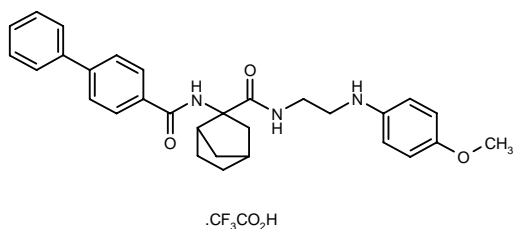
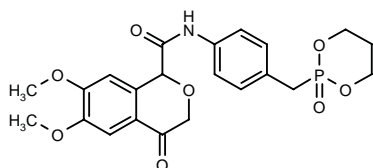


C29 H35 N3 O4; Mol wt: 489.6125

ACTION – Cathepsin K inhibitor, potentially useful for the treatment of diseases involving elevated levels of cathepsin K and particularly for the treatment or prevention of osteoporosis. A representative compound from a series of amino acid-arylaminooalkylamides, wherein the following are also included:

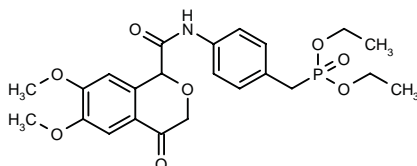
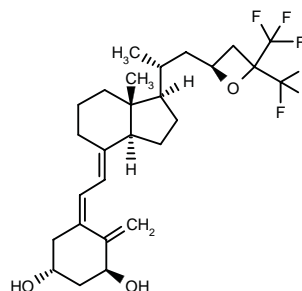


Compound	R1	R2	R3	R4	Formula
293710	OCH2Ph	H	i-Bu	3-Me-Ph	C ₂₃ H ₃₁ N ₃ O ₃
293711	OCH2Ph	-(CH2)5-		1-Naph	C ₂₇ H ₃₁ N ₃ O ₃
293712	4-(4-MeO-Ph)- -1-Piz-CH2	H	i-Bu	4-MeO-Ph	C ₂₈ H ₄₁ N ₃ O ₄
293713	OCH2Ph	-(CH2)5-		4-(4-morpholinyl- -CH2CH2O)-Ph	C ₂₉ H ₄₀ N ₄ O ₅
293714	OCH2Ph	-(CH2)5-		4-(cyclopropyl- -CH2O)-Ph	C ₂₇ H ₃₅ N ₃ O ₄
293715	OCH2Ph	-(CH2)5-		4-(1-Me-4-Pip-O)-Ph	C ₂₉ H ₄₀ N ₄ O ₄
293716	2-benzofuryl	H	i-Bu	4-i-PrO-Ph	C ₂₆ H ₃₃ N ₃ O ₄
293717	1-Me-2-indolyl	-(CH2)5-		4-i-BuO-Ph	C ₂₉ H ₃₈ N ₃ O ₃
293718	4-(4-Me-1-Piz)-Ph	-(CH2)5-		4-(4-F-PhCH2O)-Ph	C ₃₄ H ₄₂ FN ₃ O ₃
293719	4-N(Et)2-Ph	-(CH2)5-		4-(cyclopentyl-O)-Ph	C ₃₁ H ₄₄ N ₃ O ₃
293721	4-(5-Me- -3-Pyr-CH2)-Ph	H	i-Bu	4-MeO-Ph	C ₂₉ H ₃₆ N ₄ O ₃
293722	4-(4-Cl-PhO)-Ph	H	i-Bu	4-MeO-Ph	C ₂₈ H ₃₂ ClN ₃ O ₄

**293720:** C32 H34 F3 N3 O5*SOURCE* – Novartis.*REFERENCES*1. Altmann, E. et al. (Novartis AG) *Arylaminoalkylamides*. WO 0048993.**293799**6,7-Dimethoxy-4-oxo-*N*-[4-(2-oxo-1,3,2-dioxaphosphinan-2-ylmethyl)phenyl]-3,4-dihydro-1*H*-2-benzopyran-1-carboxamide

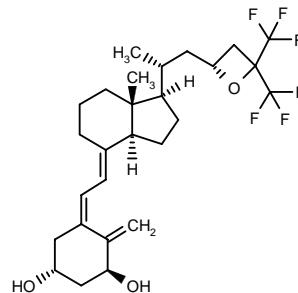
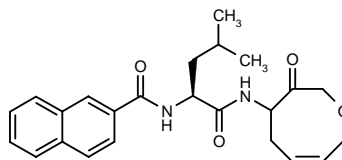
C22 H24 N O8 P; Mol wt: 461.4046

ACTION – Agent with osteogenesis- and chondrogenesis-accelerating effects whose activity was demonstrated by a significant increase in alkaline phosphatase activity in rat femoral bone marrow cells following culture at a concentration of 10 μM. Another exemplified oxygen-containing heterocyclic compound is:

**293800:** C23 H28 N O8 P*SOURCE* – Takeda.*REFERENCES*1. Anma, T. et al. (Takeda Chemical Industries, Ltd.) *Oxygen-containing heterocyclic cpds., their preparation method, and use*. JP 2000198780.**293880**23(*S*),25-Epoxy-26,26,26,27,27,27-hexafluoro-1α-hydroxyvitamin D₃

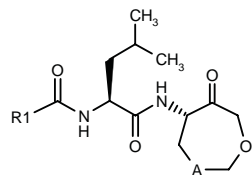
C27 H36 F6 O3; Mol wt: 522.5664

ACTION – Vitamin D analogue with the ability to promote osteogenesis and inhibit bone resorption. The compound showed binding affinity for the 1,25-dihydroxyvitamin D₃ receptor and induced differentiation of human myelogenous leukemia HL-60 cells. Another exemplified compound is:

**293881:** C27 H36 F6 O3*SOURCE* – Sumitomo Pharmaceuticals.*REFERENCES*1. Ikeda, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Vitamin D derivs*. JP 2000219630.**293989***N*²-(2-Naphthylcarbonyl)-*N*¹-(3-oxo-3,4,5,8-tetrahydro-2*H*-oxocin-4-yl)-L-leucinamide

C24 H28 N2 O4; Mol wt: 408.4952

ACTION – An inhibitor of cysteine proteases of the papain superfamily, particularly cathepsin K, with potential for the treatment of disorders characterized by excessive bone or cartilage loss or matrix degradation such as osteoporosis, gingivitis, periodontitis, osteoarthritis and rheumatoid arthritis. Other specifically claimed compounds from this series of 7-14-membered ring ether derivatives are:



Compound	R1	A	Formula
293990	2-benzothieryl	-CH=CH-	C ₂₂ H ₂₆ N ₂ O ₄ S
293991	3-Me-2-benzofuryl	-CH=CH-	C ₂₃ H ₂₆ N ₂ O ₅
293992	2-quinoxaliny	-CH=CH-	C ₂₂ H ₂₆ N ₄ O ₄
293993	2-benzofuryl	-CH=CH-	C ₂₂ H ₂₆ N ₂ O ₅
293994	2-benzothieryl	-(CH ₂) ₂ -	C ₂₂ H ₂₈ N ₂ O ₄ S
293995	5-(4-CF ₃ -Ph)-2-benzofuryl	-(CH ₂) ₂ -	C ₂₉ H ₃₁ F ₃ N ₂ O ₅
293996	1-Me-2-indolyl	-(CH ₂) ₂ -	C ₂₃ H ₃₁ N ₃ O ₄
293997	3-Me-2-benzofuryl	-(CH ₂) ₂ -	C ₂₃ H ₃₀ N ₂ O ₅
293998	2-quinoxaliny	-(CH ₂) ₂ -	C ₂₂ H ₂₈ N ₄ O ₄
293999	4-MeO-2-quinolyl	-(CH ₂) ₂ -	C ₂₄ H ₃₁ N ₃ O ₅
294000	5-Me-2-benzothieryl	-(CH ₂) ₂ -	C ₂₃ H ₃₀ N ₂ O ₄ S
294001	2-benzofuryl	-(CH ₂) ₂ -	C ₂₂ H ₂₈ N ₂ O ₅
294002	5,6-(MeO)2-2-benzofuryl	-CH ₂ -	C ₂₃ H ₃₀ N ₂ O ₇

SOURCE – GlaxoSmithKline.

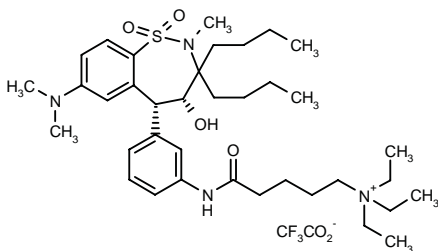
REFERENCES

1. Marquis, R.W. Jr. and Veber, D.F. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 0049011.

TREATMENT OF LIPOPROTEIN DISORDERS

293463

5-[3-[3,3-Dibutyl-7-(dimethylamino)-4(R)-hydroxy-2-methyl-1,1-dioxo-2,3,4,5-tetrahydro-1H-1,2-benzothiazepin-5(R)-yl]phenylamino]-N,N,N-triethyl-5-oxo-1-pentana-minium trifluoroacetate



C37 H61 N4 O4 S . C2 F3 O2; Mol wt: 770.9929

ACTION – Inhibitor of ileal bile acid transport (IBAT) and taurocholate uptake found to inhibit IBAT-mediated [¹⁴C]-taurocholate uptake in H14 cells with an IC₅₀ of 0.083 μM; when the same assay was performed with labeled alanine, the IC₅₀ was > 100 μM. In studies in rats, it produced a dose-dependent increase in fecal bile acid concentration. Potentially useful for the treatment of hyperlipidemic conditions and related disorders such as atherosclerosis and hypercholesterolemia.

SOURCE – Pharmacia.

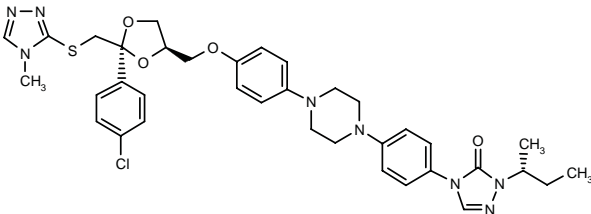
REFERENCES

1. Tollefson, M.B. et al. (Pharmacia Corp.) *Novel 1,2-benzothiazepines having activity as inhibitors of ileal bile acid transport and taurocholate uptake*. WO 0047568.

R-103757

293374

4-[4-[4-[4-[(2S,4R)-2-(4-Chlorophenyl)-2-(4-methyl-4H-1,2,4-triazol-3-ylsulfanylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl]piperazin-1-yl]phenyl]-2-[1(R)-methylpropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



C36 H41 Cl N8 O4 S; Mol wt: 717.2909

ACTION – Lipid-lowering agent, an inhibitor of microsomal triglyceride transfer protein (MTP; IC₅₀ = 6.2 and 75 nM, respectively, against protein from human and dog liver microsomes). It strongly inhibited the secretion of apolipoprotein (apo) B but not apoA by HepG2 cells (IC₅₀ = 27 and > 10,000 nM, respectively). When given orally to normolipidemic dogs, compound decreased plasma cholesterol, phospholipid and triglycerides in a time- and dose-dependent manner (ED₅₀ = 1.8, 2.1 and 3 mg/kg, respectively).

SOURCE – Janssen.

REFERENCES

1. De Conde, V.F.V. et al. (Janssen Pharmaceutica NV) *Pellets having a core coated with a lipid lowering agent and a polymer*. WO 9955313.

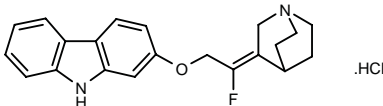
2. Heeres, J. et al. (Janssen Pharmaceutica NV) *Apolipoprotein-B synthesis inhibitors*. EP 0788496, JP 1997511759, US 5521186, US 5929075, WO 9613499.

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YM-53601*

241757

(E)-2-[2-Fluoro-2-(quinuclidin-3-ylidene)ethoxy]-9H-carbazole hydrochloride



C21 H21 F N2 O . HCl; Mol wt: 372.8688

ACTION – Hypolipidemic agent, a squalene synthase inhibitor (IC_{50} = 90, 170, 46, 45 and 79 nM in hepatic microsomes from rat, hamster, guinea pig, rhesus monkey and human HepG2 cells, respectively). In rats, compound reduced plasma cholesterol synthesis (ED_{50} = 32 mg/kg p.o.) and consequently the plasma cholesterol levels in animals fed a high-fat diet (44% reduction in non-HDL cholesterol at 50 mg/kg/day p.o. for 7 days). In hamsters, it markedly reduced plasma cholesterol and triglyceride levels in a dose-dependent fashion, with a maximum effect at the dose of 100 mg/kg/day p.o. for 7 days (76 and 73% reduction in non-HDL cholesterol and triglycerides, respectively), greater than that of the same dose of fenofibrate (respective 36 and 53% reductions). Potentially useful for the treatment of hypercholesterolemia and hypertriglyceridemia.

SOURCE – Yamanouchi.

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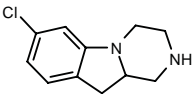
2. Ugawa, T. et al. *YM-53601, a novel squalene synthase inhibitor, reduces plasma cholesterol and triglyceride levels in several animal species*. Br J Pharmacol 2000, 131(1): 63.

*Identified compound **241757** Drug Data Rep 1997, 019(02): 0186.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

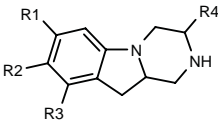
293110

7-Chloro-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole



C11 H13 Cl N2; Mol wt: 208.6907

ACTION – Agent for the treatment of obesity, as well as CNS disorders, damage to the CNS, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus and sleep apnea, a 5-HT₂ receptor ligand with K_i values of 31, 32 and 53 nM, respectively, for 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptors in binding assays. When tested in functional assays, compound gave EC_{50} values for human 5-HT_{2A} and 5-HT_{2C} receptors cloned in CHO cells of 513 and 18 nM, respectively, and relative efficacies (5-HT = 100%) of 53 and 91%, respectively. *In vivo*, it induced a specific 5-HT_{2C} syndrome in rats, maintaining significant pharmacological activity for at least 180 min after an s.c. dose of 1 mg/kg, and regulated feeding behavior in food-deprived animals, with significant hypophagia 3 h after the same dose. Other compounds from this series of pyrazino(aza)indole derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
293111	H	H	Cl	H		C ₁₁ H ₁₃ ClN ₂
293112	Cl	Me	H	H		C ₁₂ H ₁₅ ClN ₂
293113	Cl	H	H	H	10aR	C ₁₁ H ₁₃ ClN ₂
293114	Br	H	H	H		C ₁₁ H ₁₃ BrN ₂
293116	H	Cl	H	H	10aR	C ₁₁ H ₁₃ ClN ₂
293117	Cl	H	H	Me	3R,10aR	C ₁₂ H ₁₅ ClN ₂
293118	Cl	H	H	Me	3S,10aR	C ₁₂ H ₁₅ ClN ₂

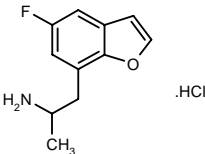
SOURCE – Vernalis Research.

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1. Adams, D.R. et al. (Vernalis Research Ltd.) *Pyrazino(aza)indole derivs*. WO 0044753.

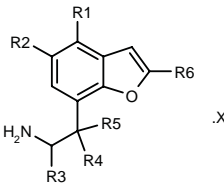
293130

1-(5-Fluorobenzofuran-7-yl)propan-2-amine hydrochloride



C11 H12 F N O . HCl; Mol wt: 229.6807

ACTION – 5-HT_{2C} receptor agonist particularly useful for the treatment of obesity. A representative compound from a series of aminoalkylbenzofurans, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
293131	H	F	(S)-Me	H	H	H	HCl	C ₁₁ H ₁₂ FNO.HCl
293132	H	F	(R)-Me	H	H	H	HCl	C ₁₁ H ₁₂ FNO.HCl
293133	H	F	H	Me	Me	H	HCl	C ₁₂ H ₁₄ FNO.HCl
293134	H	CONH2	Me	H	H	H	HCl	C ₁₂ H ₁₄ N ₂ O ₂ .HCl
293136	H	CF3	(R)-Me	H	H	H	HCl	C ₁₂ H ₁₂ F ₃ NO.HCl
293140	H	F	H	H	Et	H	oxalate	C ₁₂ H ₁₄ FNO.C ₂ H ₂ O ₄
293142	H	F	(S)-Me	H	H	Br	HCl	C ₁₁ H ₁₁ BrFNO.HCl
293144	H	F	H	H	Me	H		C ₁₁ H ₁₂ FNO
293147	H	CONHBu	Me	H	H	H	HCl	C ₁₆ H ₂₂ N ₂ O ₂ .HCl
293149	CF3	H	Me	H	H	H	HCl	C ₁₂ H ₁₂ F ₃ NO.HCl

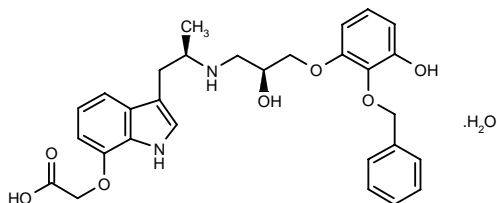
SOURCE – Lilly.

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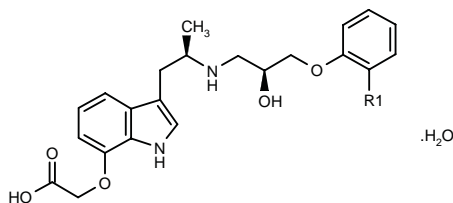
293297

2-[3-[2(*R*)-[3-(2-Benzoyloxy-3-hydroxyphenoxy)-2(*S*)-hydroxypropylamino]propyl]-1*H*-indol-7-yloxy]acetic acid hydrate



C29 H32 N2 O7 · H2O; Mol wt: 538.5936

ACTION – Agent for the treatment of obesity and diabetes, a potent human β_3 -adrenoceptor agonist (EC_{50} = 0.16 nM for stimulation of cAMP in CHO cells transfected with the human receptor) with negligible activity against β_1 - and β_2 -adrenoceptors. Within this series of 3,7-disubstituted indole derivatives, the following are also included:



Compound	R1	Formula
293298	OCH ₂ Ph	C ₂₈ H ₃₂ N ₂ O ₆ ·H ₂ O
293299	SMe	C ₂₃ H ₂₈ N ₂ O ₅ S·H ₂ O

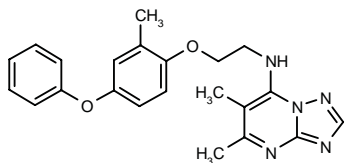
SOURCE – Dainippon Pharmaceutical.

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1. Kato, S. et al. (Dainippon Pharmaceutical Co., Ltd.) 3,7-Disubstd. indole derivs. and medicinal compns. containing the same. WO 0044721.

293359

N-(5,6-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl)-*N*-[2-(2-methyl-4-phenoxyphenoxy)ethyl]amine



C22 H23 N5 O2; Mol wt: 389.4567

ACTION – An inhibitor of fat accumulation in fat cells, as demonstrated in several *in vitro* assays, potentially useful in the treatment or prevention of obesity, diabetes and hyperlipidemia. A representative compound from a series of aminopyrimidine derivatives.

SOURCES – Sumitomo Chemical; Sumitomo Pharmaceuticals.

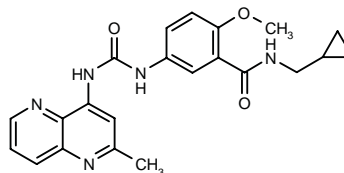
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293501

N-(Cyclopropylmethyl)-2-methoxy-5-[3-(2-methyl-1,5-naphthyridin-4-yl)ureido]benzamide

N-[3-[*N*-(Cyclopropylmethyl)carbamoyl]-4-methoxyphenyl]-*N'*-(2-methyl-1,5-naphthyridin-4-yl)urea



C22 H23 N5 O3; Mol wt: 405.4557

ACTION – A representative compound from a series of phenylurea and phenylthiourea derivatives that antagonizes the orexin receptor, particularly the orexin-1 receptor, as demonstrated in HEK293 cells expressing the human orexin-1 receptor (pK_b > 7.5). This compound is useful for the treatment of obesity including obesity in type 2 diabetes patients.

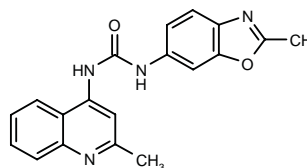
SOURCE – GlaxoSmithKline.

REFERENCES

1. Coulton, S. et al. (SmithKline Beecham plc) *Phenyl urea and phenyl thiourea derivs*. WO 0047580.

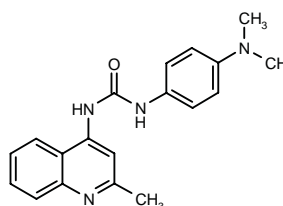
293502

N-(2-Methylbenzoxazol-6-yl)-*N'*-(2-methylquinolin-4-yl)urea



C19 H16 N4 O2; Mol wt: 332.3614

ACTION – Orexin receptor antagonist, particularly active at the orexin-1 receptor, as demonstrated in HEK293 cells expressing the human orexin-1 receptor by a pK_b value > 6.0. This compound is useful for the treatment of obesity including obesity in type 2 diabetes patients. Another compound from this series of phenylurea and phenylthiourea derivatives is:



293503: C19 H20 N4 O

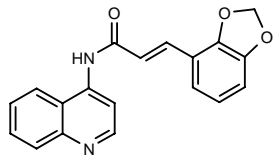
SOURCE – GlaxoSmithKline.

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1. Coulton, S. et al. (SmithKline Beecham plc) *Phenyl urea and phenyl thiourea derivs. as orexin receptor antagonists*. WO 0047577.

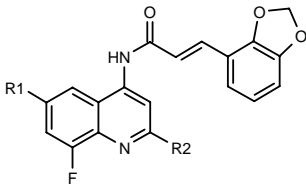
293504

3-(1,3-Benzodioxol-4-yl)-N-(4-quinolinyl)-2(E)-propen-
amide



C19 H14 N2 O3; Mol wt: 318.3306

ACTION – Orexin receptor antagonist, particularly active at the orexin-1 receptor, as demonstrated in HEK293 cells expressing the human orexin-1 receptor (pK_b > 6.5). This compound is useful for the treatment of obesity including obesity in type 2 diabetes patients. Other exemplified cin-
namide derivatives include the following:



Compound	R1	R2	Formula
293505	H	H	C ₁₉ H ₁₃ FN ₂ O ₃
293506	F	H	C ₁₉ H ₁₂ F ₂ N ₂ O ₃
293507	F	Me	C ₂₀ H ₁₄ F ₂ N ₂ O ₃

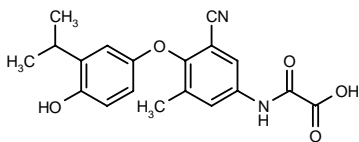
SOURCE – GlaxoSmithKline.

REFERENCES

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receptors antagonists*. WO 0047576.

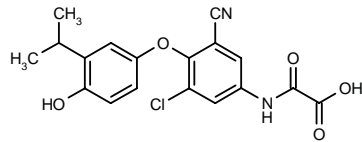
293582

N-[3-Cyano-4-(4-hydroxy-3-isopropylphenoxy)-5-methyl-
phenyl]oxamic acid



C19 H18 N2 O5; Mol wt: 354.3602

ACTION – Thyroid receptor ligand, potentially useful for the treatment of obesity, hyperlipidemia, thyroid disease, hypothyroidism and related disorders. Another specifically
claimed cyano-containing oxamic acid is:



293583: C18 H15 Cl N2 O5

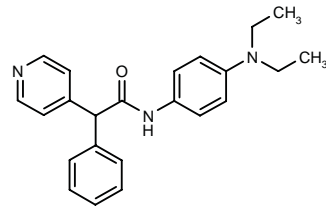
SOURCE – Pfizer.

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thyroid receptor ligands*. EP 1033364, JP 2000256299.

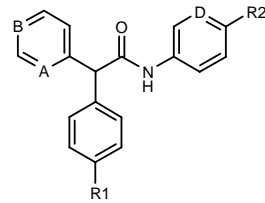
293584

N-[4-(Diethylamino)phenyl]-2-phenyl-2-(4-pyridinyl)-
acetamide



C23 H25 N3 O; Mol wt: 359.4705

ACTION – Neuropeptide Y (NPY) antagonist, expected to be useful for the treatment of disorders associated with
excess NPY including eating disorders, among others. Other specifically claimed substituted amides are:



Compound	R1	R2	A	B	D	Formula
293585	F	1-Pip	CH	N	N	C ₂₃ H ₂₃ FN ₄ O
293586	H	1-Pip	CH	N	N	C ₂₃ H ₂₄ N ₄ O
293587	H	N(Et)2	N	CH	CH	C ₂₃ H ₂₅ N ₃ O
293588	H	N(Et)2	CH	CH	N	C ₂₃ H ₂₅ N ₃ O
293589	H	SO2N(Et)2	CH	N	CH	C ₂₃ H ₂₅ N ₃ O ₃ S
293590	H	1-pyrrolidinyl	CH	CH	N	C ₂₃ H ₂₃ N ₃ O
293591	H	1-Pip	CH	CH	N	C ₂₄ H ₂₅ N ₃ O
293592	H	2,5-(Me)2- -1-pyrrolidinyl	CH	CH	N	C ₂₅ H ₂₇ N ₃ O
293593	H	SO2N(Et)2	CH	CH	N	C ₂₃ H ₂₅ N ₃ O ₃ S
293594	H	SO2N(Me)2	CH	CH	N	C ₂₁ H ₂₁ N ₃ O ₃ S

SOURCE – Pfizer.

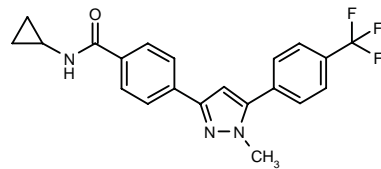
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(NPY) antagonists*. EP 1033366, JP 2000239243.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

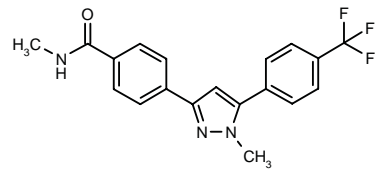
293202

N-Cyclopropyl-4-[1-methyl-5-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-3-yl]benzamide



C21 H18 F3 N3 O; Mol wt: 385.3872

ACTION – Agent for the treatment or prevention of anemia that acts by stimulating erythropoiesis. *In vitro*, compound produced a 60% increase in human erythrocyte precursor cell proliferation at 10 μM. Another specifically claimed compound from this series of pyrazole alkylamides is:



293203: C19 H16 F3 N3 O

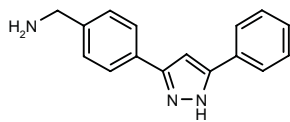
SOURCE – Bayer.

REFERENCES

1. Stoltefuss, J. et al. (Bayer AG) *Pyrazole alkylamides*. DE 19904391, WO 0046207.

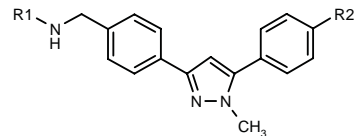
293204

N-[4-(5-Phenyl-1*H*-pyrazol-3-yl)benzyl]amine



C16 H15 N3; Mol wt: 249.3155

ACTION – Agent for the treatment or prevention of anemia that acts by stimulating erythropoiesis. Other specifically claimed compounds from this series of substituted pyrazole benzyl amine derivatives are:



Compound	R1	R2	Formula
293205	Ac	H	C ₁₉ H ₁₉ N ₃ O
293206	H	CF ₃	C ₁₈ H ₁₆ F ₃ N ₃
293207	Ac	Br	C ₁₉ H ₁₈ BrN ₃ O
293208	Ac	CF ₃	C ₂₀ H ₁₈ F ₃ N ₃ O

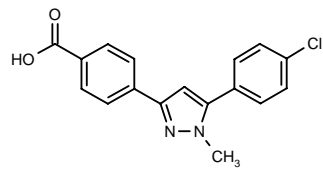
SOURCE – Bayer.

REFERENCES

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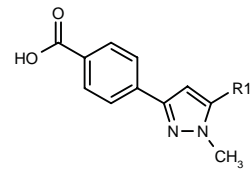
293209

4-[5-(4-Chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]benzoic acid



C17 H13 Cl N2 O2; Mol wt: 312.7547

ACTION – Agent for the treatment or prevention of anemias that acts by stimulating erythropoiesis. *In vitro*, compound produced an 85% increase in human erythrocyte precursor cell proliferation at 10 μM. Other specifically claimed compounds from this series of pyrazole carboxylic acids are:



Compound	R1	Formula
293210	4-CF ₃ -Ph	C ₁₈ H ₁₃ F ₃ N ₂ O ₂
293211	2-Pyr	C ₁₆ H ₁₃ N ₃ O ₂
293212	4-F-Ph	C ₁₇ H ₁₃ FN ₂ O ₂
293213	2-thienyl	C ₁₅ H ₁₂ N ₂ O ₂ S

SOURCE – Bayer.

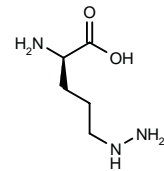
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TREATMENT OF DISORDERS OF
PURINE AND PYRIMIDINE
METABOLISM

293879

2(*R*)-Amino-5-hydrazinopentanoic acid



C5 H13 N3 O2; Mol wt: 147.1767

ACTION – Agent for the treatment of hyperammonemia that acts by inhibiting the enzyme ornithine aminotransferase (about 40% inhibition at 0.05-0.5 mM). It inhibited the increase in hepatic ammonia by 51% at 100 mg/kg i.p. in mice defective in ornithine carbamoyltransferase.

SOURCE – Taiho.

REFERENCES

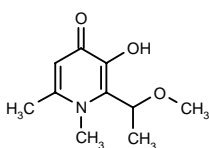
1. Saeki, T. et al. (Taiho Pharmaceutical Co., Ltd.) *N^δ-Substd. aminoornithine derivs. and their salts*. JP 2000219663.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

APO-363

295324

3-Hydroxy-2-(1-methoxyethyl)-1,6-dimethyl-1,4-dihydropyridin-4-one



C10 H15 N O3; Mol wt: 197.2325

ACTION – Orally active, second-generation iron chelator with linear pharmacokinetics after i.v. and p.o. administration in rats (25, 75 and 250 mg/kg), extensive distribution, low plasma protein binding and a long terminal half-life (about 7 h), and an absolute oral bioavailability of 93%. Urinary and fecal recovery of unchanged drug accounted for only 14-20% of the dose, while the glucuronide, the major metabolite, accounted for 40-60% of dose. Potentially useful for the treatment of disorders associated with iron distribution such as thalassemia.

SOURCES – Apotex; BTG.

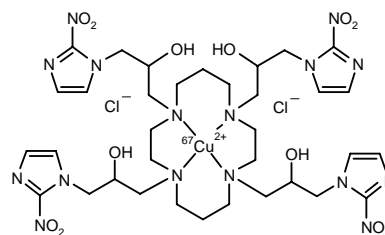
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3. Guo, F. et al. *Testing the compartmental and non-compartmental pharmacokinetic consistency of APO363 following intravenous and oral administration in the rat*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3491.

DIAGNOSTIC AGENTS

292773

(*SP-4-1*)-[$\alpha, \alpha', \alpha'', \alpha'''$]-Tetrakis(2-nitro-1*H*-imidazol-1-ylmethyl)-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraethanol- $\kappa N^1, \kappa N^4, \kappa N^8, \kappa N^{11}$]copper(2+)-67Cu dichloride



C34 H52 Cl2 Cu N16 O12; Mol wt: 1014.7910

ACTION – A representative compound from a series of 1,4,8,11-tetraazacyclotetradecane (cyclam) derivatives that form radionuclide metal-containing complexes and are useful as radiodiagnostic agents. This complex demonstrated hypoxic cell selectivity and retention, being recovered from hypoxic tumors at a level about 3-fold higher than from nonhypoxic, well-oxygenated tumors. Potentially useful for imaging and noninvasively determining tissue hypoxia and radioresistance of tumors.

SOURCE – Fox Chase Cancer Center, Philadelphia, PA (US).

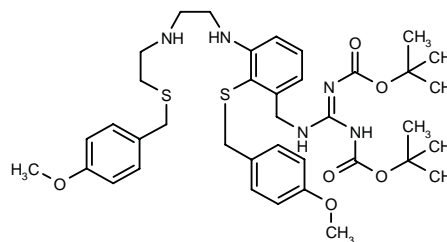
REFERENCES

1. Chapman, J.D. et al. (Fox Chase Cancer Center) *1,4,8,11-Tetraazacyclotetradecane derivs. as radiodiagnostic agents and their use in determining hypoxia and radioresistance of tumors*. WO 0043004.

DRD-269

293126

*N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*³-[2-(4-methoxybenzylsulfanyl)-3-[2-[2-(4-methoxybenzylsulfanyl)-ethylamino]ethylamino]benzyl]guanidine



C38 H53 N5 O6 S2; Mol wt: 739.9977

ACTION – A representative compound from a series of aralkylguanidines which when labeled with radioactive technetium (^{99m}Tc) exhibits high accumulation in the heart and is thus useful for heart imaging.

ACTION – Agent for the treatment of hyperammonemia that acts by inhibiting the enzyme ornithine aminotransferase (about 40% inhibition at 0.05-0.5 mM). It inhibited the increase in hepatic ammonia by 51% at 100 mg/kg i.p. in mice defective in ornithine carbamoyltransferase.

SOURCE – Taiho.

REFERENCES

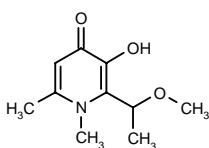
1. Saeki, T. et al. (Taiho Pharmaceutical Co., Ltd.) *N^δ-Substd. aminoornithine derivs. and their salts*. JP 2000219663.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

APO-363

295324

3-Hydroxy-2-(1-methoxyethyl)-1,6-dimethyl-1,4-dihydropyridin-4-one



C10 H15 N O3; Mol wt: 197.2325

ACTION – Orally active, second-generation iron chelator with linear pharmacokinetics after i.v. and p.o. administration in rats (25, 75 and 250 mg/kg), extensive distribution, low plasma protein binding and a long terminal half-life (about 7 h), and an absolute oral bioavailability of 93%. Urinary and fecal recovery of unchanged drug accounted for only 14-20% of the dose, while the glucuronide, the major metabolite, accounted for 40-60% of dose. Potentially useful for the treatment of disorders associated with iron distribution such as thalassemia.

SOURCES – Apotex; BTG.

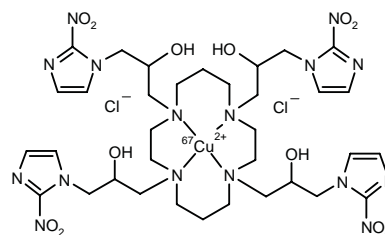
REFERENCES

1. Hider, R.C. et al. (BTG International Ltd.) *Novel orally active iron (III) chelators*. WO 9854138.
2. Guo, F. et al. *Development of a high-performance liquid chromatography (HPLC) assay for determination of a second-generation novel oral iron chelator (APO363) in biological fluids and its application to pharmacokinetics in rats*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 1022.
3. Guo, F. et al. *Testing the compartmental and non-compartmental pharmacokinetic consistency of APO363 following intravenous and oral administration in the rat*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3491.

DIAGNOSTIC AGENTS

292773

(*SP-4-1*)-[$\alpha, \alpha', \alpha'', \alpha'''$]-Tetrakis(2-nitro-1*H*-imidazol-1-ylmethyl)-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraethanol- $\kappa N^1, \kappa N^4, \kappa N^8, \kappa N^{11}$]copper(2+)-67Cu dichloride



C34 H52 Cl2 Cu N16 O12; Mol wt: 1014.7910

ACTION – A representative compound from a series of 1,4,8,11-tetraazacyclotetradecane (cyclam) derivatives that form radionuclide metal-containing complexes and are useful as radiodiagnostic agents. This complex demonstrated hypoxic cell selectivity and retention, being recovered from hypoxic tumors at a level about 3-fold higher than from nonhypoxic, well-oxygenated tumors. Potentially useful for imaging and noninvasively determining tissue hypoxia and radioresistance of tumors.

SOURCE – Fox Chase Cancer Center, Philadelphia, PA (US).

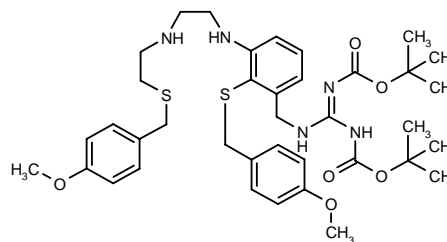
REFERENCES

1. Chapman, J.D. et al. (Fox Chase Cancer Center) *1,4,8,11-Tetraazacyclotetradecane derivs. as radiodiagnostic agents and their use in determining hypoxia and radioresistance of tumors*. WO 0043004.

DRD-269

293126

*N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*³-[2-(4-methoxybenzylsulfanyl)-3-[2-[2-(4-methoxybenzylsulfanyl)-ethylamino]ethylamino]benzyl]guanidine



C38 H53 N5 O6 S2; Mol wt: 739.9977

ACTION – A representative compound from a series of aralkylguanidines which when labeled with radioactive technetium (^{99m}Tc) exhibits high accumulation in the heart and is thus useful for heart imaging.

ACTION – Agent for the treatment of hyperammonemia that acts by inhibiting the enzyme ornithine aminotransferase (about 40% inhibition at 0.05-0.5 mM). It inhibited the increase in hepatic ammonia by 51% at 100 mg/kg i.p. in mice defective in ornithine carbamoyltransferase.

SOURCE – Taiho.

REFERENCES

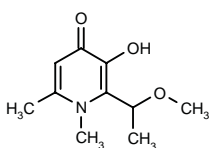
1. Saeki, T. et al. (Taiho Pharmaceutical Co., Ltd.) *N^δ-Substd. aminoornithine derivs. and their salts*. JP 2000219663.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

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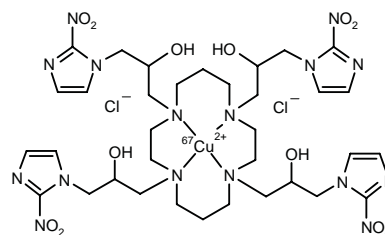
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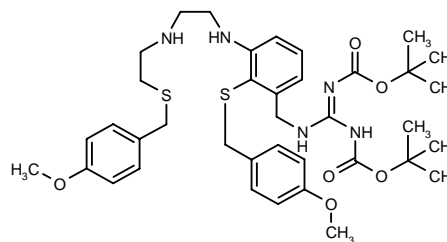
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DRD-269

293126

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ACTION – A representative compound from a series of aralkylguanidines which when labeled with radioactive technetium (^{99m}Tc) exhibits high accumulation in the heart and is thus useful for heart imaging.

SOURCE – Daiichi Radioisotope.

REFERENCES

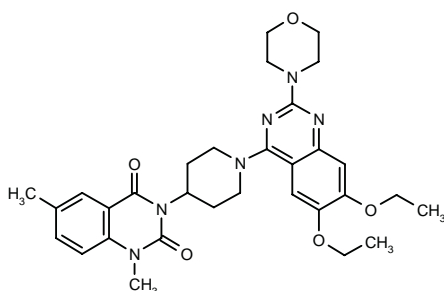
1. Kagotani, H. et al. (Daiichi Radioisotope Labs., Ltd.) *Novel aralkylguanidine cpds.* JP 2000219674, WO 0044715.

PHARMACOLOGICAL TOOLS

KF-24345²⁻⁵

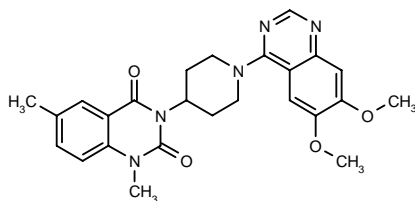
244470

3-[1-[6,7-Diethoxy-2-(4-morpholinyl)quinazolin-4-yl]piperidin-4-yl]-1,6-dimethylquinazolin-2,4(1*H*,3*H*)-dione



C31 H38 N6 O5; Mol wt: 574.6782

ACTION – Adenosine transporter inhibitor with a K_i of 2 nM for inhibition of [3 H]-NBI binding in guinea pig brain and an IC_{50} value of 61 nM for inhibition of adenosine uptake in human erythrocytes. Also reported to produce potent and sustained inhibition of [3 H]-adenosine uptake into murine erythrocytes *ex vivo* following oral administration. Selected for further evaluation and claimed to be potentially useful for protecting the myocardium and for preventing or treating inflammation such as leg and foot edema. Also potentially useful as a tool to elucidate the pharmacological and physiological roles of the adenosine transporter. Another compound with a similar profile is:



KF-21652 [293884]:^{1,5} C25 H27 N5 O4

SOURCE – Kyowa Hakko.

REFERENCES

1. Fujiwara, S. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Adenosine incorporation inhibitor.* EP 0638567, JP 1995518811, US 5605900, US 5624926, US 5648353, US 5658917, WO 9419342.

2. Fujiwara, S. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Quinazoline deriv.* EP 0726267, JP 1997165385, US 5948784, WO 9606841.

3. Fujiwara, S. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Therapeutic agent for kidney diseases.* WO 9729749.

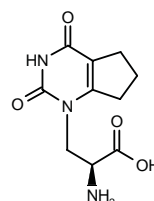
4. Okamura, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Use of adenosine uptake inhibitors for the manufacture of a medicament for the treatment of pancreatitis.* EP 0870502, JP 1998338635.

5. *Synthesis and evaluation of adenosine transporter inhibitors.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PC-19.

(S)-CPW-399

293831

2(*S*)-Amino-3-(2,4-dioxo-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl)propionic acid



C10 H13 N3 O4; Mol wt: 239.2297

ACTION – Selective AMPA receptor agonist (IC_{50} = 800 nM) with low affinity for kainate receptors and inactive at NMDA receptors and the associated glycine site. In mouse cerebellar granule cell cultures, compound was able to stimulate an increase in intracellular Ca^{2+} concentration and to induce neuronal cell death in a time- and concentration-dependent manner (EC_{50} = 100 μ M after 24-h exposure). The neurotoxic effect was completely abolished by coexposure to the AMPA receptor antagonist NBQX and the AMPA/kainate receptor antagonist CNQX, but was unaffected by an NMDA receptor antagonist. Potential pharmacological tool to elucidate the role of the AMPA receptor in physiological and pathological brain processes.

SOURCES – Istituto di Richerche Farmacologiche Mario Negri, Milano (IT); University of St. Andrews, St. Andrews (GB); Università degli Studi di Salerno, Salerno (IT); Università degli Studi di Siena, Siena (IT).

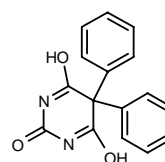
REFERENCES

1. Morelli, E. et al. *Synthesis, biochemical pharmacology, and evaluation of the excitotoxic efficacy of (S)-CPW399, a novel and selective AMPA agonist.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-100.

PD-0007258

293971

4,6-Dihydroxy-5,5-diphenylpyrimidin-2(5*H*)-one



C16 H12 N2 O3; Mol wt: 280.2818

SOURCE – Daiichi Radioisotope.

REFERENCES

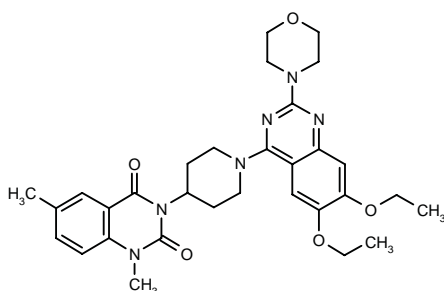
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PHARMACOLOGICAL TOOLS

KF-24345²⁻⁵

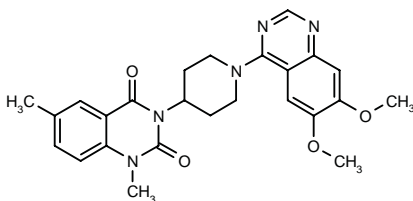
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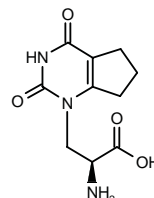
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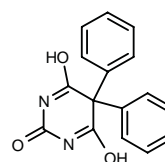
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1. Morelli, E. et al. *Synthesis, biochemical pharmacology, and evaluation of the excitotoxic efficacy of (S)-CPW399, a novel and selective AMPA agonist.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-100.

PD-0007258

293971

4,6-Dihydroxy-5,5-diphenylpyrimidin-2(5*H*)-one



C16 H12 N2 O3; Mol wt: 280.2818

ACTION – Selective inhibitor of the catalytic domain of the membrane-type matrix metalloproteinase MT1-MMP (MMP-14), with an IC_{50} value of 0.78 μ M versus at least 5-fold higher values for other MMPs. Compound acted as a competitive inhibitor of the enzyme ($K_i = 0.58 \mu$ M) and may be useful as a tool for elucidating the role of this enzyme in physiological and pathological conditions.

SOURCE – Pfizer.

REFERENCES

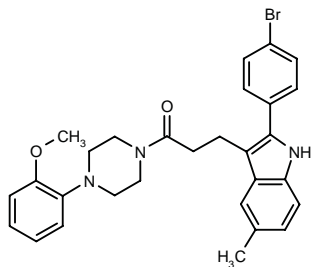
1. Wang, Y. et al. *A selective, small molecule inhibitor of MT1-MMP catalytic domain.* Inflamm Res 2000, 49(Suppl. 2): S98.
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ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

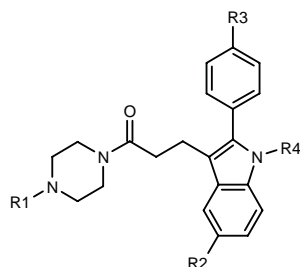
294578

3-[2-(4-Bromophenyl)-5-methyl-1*H*-indol-3-yl]-1-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one



C29 H30 Br N3 O2; Mol wt: 532.4790

ACTION – Potent tachykinin, especially NK₁, receptor antagonist, potentially useful in the treatment of a variety of disorders related to an excess of substance P, preferably pain, inflammation, migraine, emesis, post-herpetic neuralgia, depression and anxiety. Other exemplified 2-arylindole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
294579	3,5-(MeO)2-Ph	Me	Br	H	C ₃₀ H ₃₂ BrN ₃ O ₃
294580	CH2Ph	Cl	Cl	Me	C ₂₉ H ₂₉ Cl ₂ N ₃ O
294581	3,5-(CF3)2-PhCH2	Cl	Cl	H	C ₃₀ H ₂₅ Cl ₂ F ₆ N ₃ O
294582	2-MeO-Ph	Me	Me	H	C ₃₀ H ₃₃ N ₃ O ₂
294583	2-MeO-Ph	Me	Cl	Me	C ₃₀ H ₃₂ ClN ₃ O ₂

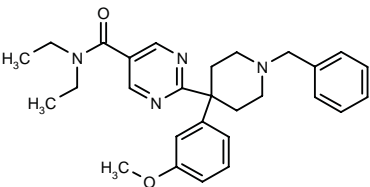
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Chapman, K.T. et al. (Merck Sharp & Dohme Ltd.) *2-Aryl indole derivs. as antagonists of tachykinins*. WO 0051984.

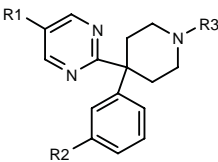
294910

2-[1-Benzyl-4-(3-methoxyphenyl)piperidin-4-yl]-*N,N*-diethylpyrimidine-5-carboxamide



C28 H34 N4 O2; Mol wt: 458.6026

ACTION – Potent and selective delta opioid receptor (DOP) ligand, potentially useful for the treatment of a variety of disorders including chronic and neurogenic pain, organ and skin graft rejection, stroke, shock, Hodgkin's disease, Sjögren's disease, systemic lupus erythematosus, gastritis, irritable bowel syndrome and inflammatory diseases such as arthritis, psoriasis, asthma and inflammatory bowel disease. Other exemplified 4,4-biarylpyperidine derivatives include the following:

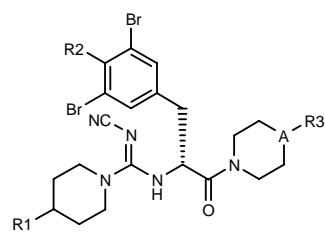


Compound	R1	R2	R3	Formula
294911	CON(Et)2	OH	H	C ₂₀ H ₂₆ N ₄ O ₂
294912	CON(Et)2	OSO2CF3	CH2CH(Me)Pr	C ₂₇ H ₃₇ F ₃ N ₄ O ₄ S
294913	CON(Et)2	CN	CH2CH(Me)Pr	C ₂₇ H ₃₇ N ₅ O
294914	CON(Et)2	5-tetrazolyl	CH2CH(Me)Pr	C ₂₇ H ₃₈ N ₆ O
294915	CON(Et)2	CH2OH	CH2CH(Me)Pr	C ₂₇ H ₄₀ N ₄ O ₂
294916	CONHC(Me)2CH2OH	OMe	CH2Ph	C ₂₈ H ₃₄ N ₄ O ₃
294917	C(Et)2OH	OMe	CH2CH(Me)Pr	C ₂₇ H ₄₁ N ₃ O ₂

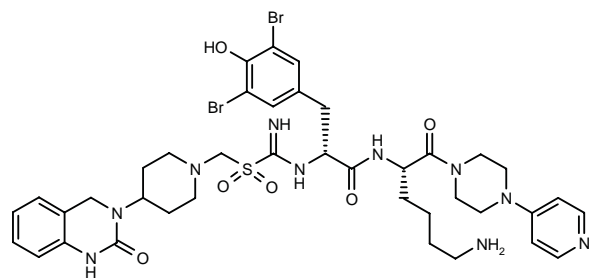
SOURCE – Pfizer.

REFERENCES

1. Liras, S. and McHardy, S.F. (Pfizer Products Inc.) *4-Phenyl-4-heteroarylpyperidine derivs. as opioid receptor ligands*. EP 1038872, JP 2000247969.



Compound	R1	R2	R3	A	Formula
295005	2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	NH2	4-Pyr	N	C ₃₃ H ₃₆ Br ₂ N ₁₀ O ₂
295006	2-oxo-2,3,4,5-tetrahydro-1H-1,3-benzodiazepin-3-yl	NH2	4-Me-1-Piz	CH	C ₃₅ H ₄₆ Br ₂ N ₁₀ O ₂
295007	3-Ph-5-oxo-4,5-dihydro-1,2,4-triazol-1-yl	OH	1-Me-4-Pip	N	C ₃₄ H ₄₂ Br ₂ N ₁₀ O ₃
295008	7-MeO-2-oxo-2,3,4,5-tetrahydro-1H-1,3-benzodiazepin-3-yl	NH2	1-Me-4-Pip	N	C ₃₆ H ₄₈ Br ₂ N ₁₀ O ₃
295009	2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-3-yl	NH2	1-Me-4-Pip	CH	C ₃₇ H ₄₄ Br ₂ N ₁₀ O ₂



295004: C39 H50 Br2 N10 O6 S

SOURCE – Boehringer Ingelheim.

REFERENCES

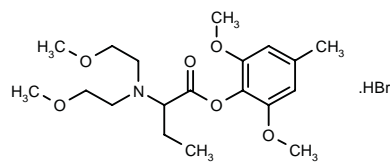
1. Eberlein, W. et al. (Boehringer Ingelheim Pharma KG) *Modified amino-acid amides as CGRP antagonists*. DE 19911039, WO 0055154.

ANESTHETIC DRUGS

ORG-25435

295068

2-[N,N-Bis(2-methoxyethyl)amino]butyric acid 4-methyl-2,6-dimethoxyphenyl ester hydrobromide



C19 H31 N O6 . HBr; Mol wt: 450.3668

ACTION – Water-soluble general anesthetic that, like propofol, acts as a positive allosteric modulator at GABA_A receptors, as demonstrated in *Xenopus* oocytes expressing human GABA_A receptors where both compounds induced a concentration-dependent enhancement of GABA-evoked currents (EC₅₀ = 10 and 4.1 μM, respectively). In mice, compound given i.v. induced a rapid loss of righting reflex and was more potent than the parent compound M&B-16753 and propofol in terms of the hypnotic dose (ED₅₀ = 21, 85.9 and 68 μmol/kg, respectively). In rats, it produced rapid induction of anesthesia and rapid return to righting. This favorable pharmaco-dynamic profile was confirmed in preliminary clinical trials in healthy volunteers.

SOURCE – Organon.

REFERENCES

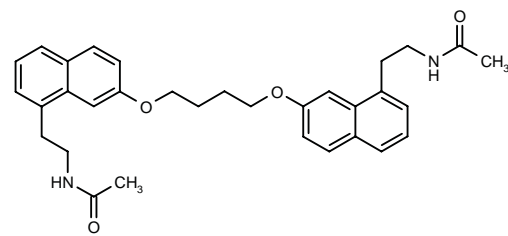
1. Hamilton, N.M. (Akzo Nobel N.V.) *α-Amino acid phenyl ester derivs*. WO 0005196.
2. Gemmell, D.K. et al. *Org 25435 - A new water-soluble intravenous anaesthetic*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 14-18, San Francisco) 2000, Abst A-749.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

294907

N-[2-[7-[4-[8-(2-Acetamidoethyl)naphthalen-2-yloxy]butoxy]naphthalen-1-yl]ethyl]acetamide



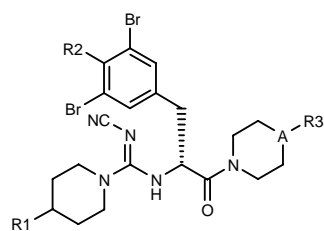
C32 H36 N2 O4; Mol wt: 512.6464

ACTION – Agent with high affinity for melatonin receptors, potentially useful for the treatment of a broad range of disorders including seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic activity and to have a potent effect on circadian rhythms via the melatonergic system in animal models. A representative compound from a series of substituted dimeric derivatives.

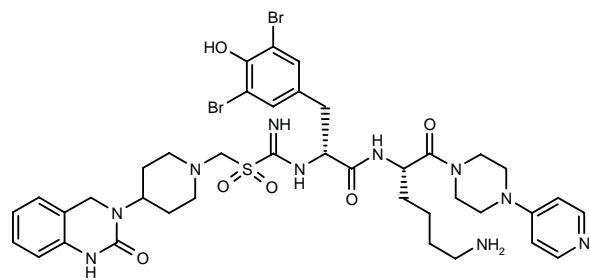
SOURCE – ADIR.

REFERENCES

1. Lesieur, D. et al. (ADIR et Cie.) *Substd. dimeric cpds., process for their preparation and pharmaceutical compsns. thereof*. EP 1038863, FR 2791344, JP 2000319242.



Compound	R1	R2	R3	A	Formula
295005	2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	NH2	4-Pyr	N	C ₃₃ H ₃₆ Br ₂ N ₁₀ O ₂
295006	2-oxo-2,3,4,5-tetrahydro-1H-1,3-benzodiazepin-3-yl	NH2	4-Me-1-Piz	CH	C ₃₅ H ₄₆ Br ₂ N ₁₀ O ₂
295007	3-Ph-5-oxo-4,5-dihydro-1,2,4-triazol-1-yl	OH	1-Me-4-Pip	N	C ₃₄ H ₄₂ Br ₂ N ₁₀ O ₃
295008	7-MeO-2-oxo-2,3,4,5-tetrahydro-1H-1,3-benzodiazepin-3-yl	NH2	1-Me-4-Pip	N	C ₃₆ H ₄₈ Br ₂ N ₁₀ O ₃
295009	2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-3-yl	NH2	1-Me-4-Pip	CH	C ₃₇ H ₄₄ Br ₂ N ₁₀ O ₂



295004: C39 H50 Br2 N10 O6 S

SOURCE – Boehringer Ingelheim.

REFERENCES

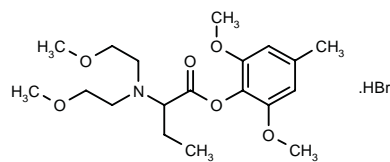
1. Eberlein, W. et al. (Boehringer Ingelheim Pharma KG) *Modified amino-acid amides as CGRP antagonists*. DE 19911039, WO 0055154.

ANESTHETIC DRUGS

ORG-25435

295068

2-[N,N-Bis(2-methoxyethyl)amino]butyric acid 4-methyl-2,6-dimethoxyphenyl ester hydrobromide



C19 H31 N O6 . HBr; Mol wt: 450.3668

ACTION – Water-soluble general anesthetic that, like propofol, acts as a positive allosteric modulator at GABA_A receptors, as demonstrated in *Xenopus* oocytes expressing human GABA_A receptors where both compounds induced a concentration-dependent enhancement of GABA-evoked currents (EC₅₀ = 10 and 4.1 μM, respectively). In mice, compound given i.v. induced a rapid loss of righting reflex and was more potent than the parent compound M&B-16753 and propofol in terms of the hypnotic dose (ED₅₀ = 21, 85.9 and 68 μmol/kg, respectively). In rats, it produced rapid induction of anesthesia and rapid return to righting. This favorable pharmaco-dynamic profile was confirmed in preliminary clinical trials in healthy volunteers.

SOURCE – Organon.

REFERENCES

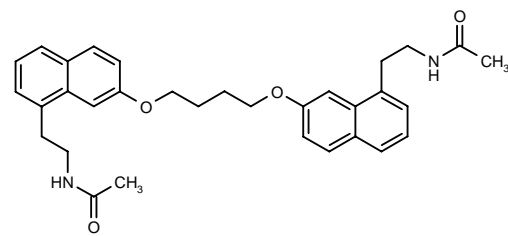
1. Hamilton, N.M. (Akzo Nobel N.V.) *α-Amino acid phenyl ester derivs*. WO 0005196.
2. Gemmell, D.K. et al. *Org 25435 - A new water-soluble intravenous anaesthetic*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 14-18, San Francisco) 2000, Abst A-749.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

294907

N-[2-[7-[4-[8-(2-Acetamidoethyl)naphthalen-2-yloxy]butoxy]naphthalen-1-yl]ethyl]acetamide



C32 H36 N2 O4; Mol wt: 512.6464

ACTION – Agent with high affinity for melatonin receptors, potentially useful for the treatment of a broad range of disorders including seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic activity and to have a potent effect on circadian rhythms via the melatonergic system in animal models. A representative compound from a series of substituted dimeric derivatives.

SOURCE – ADIR.

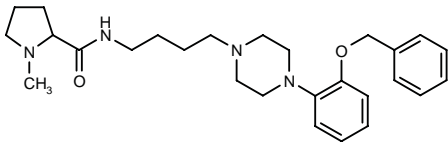
REFERENCES

1. Lesieur, D. et al. (ADIR et Cie.) *Substd. dimeric cpds., process for their preparation and pharmaceutical compsns. thereof*. EP 1038863, FR 2791344, JP 2000319242.

ANXIOLYTICS

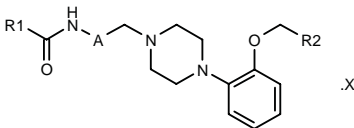
294365

N-[4-[4-(2-Benzyloxyphenyl)piperazin-1-yl]butyl]-1-methylpyrrolidine-2-carboxamide



C27 H38 N4 O2; Mol wt: 450.6232

ACTION – Dual-action compound that acts as a 5-HT_{1A} receptor agonist and 5-HT₂ receptor antagonist and is thus useful for the treatment of psychoneurological disorders such as anxiety, depression, dementia or motion sickness. It exhibited IC₅₀ values of 0.5 and 5.7 nM in binding assays using rat 5-HT_{1A} and 5-HT₂ receptors, respectively. The compound attenuated the DOI-induced head twitch response (ED₅₀ = 2.9 mg/kg p.o.) and inhibited scopolamine- and ketamine-induced motor deficits in mice (MED = 3 mg/kg p.o.). Other exemplified compounds are:



Compound	R1	R2	A	X	Formula
294367	2-pyrrolidinyl	Ph	-(CH2)3-		C ₂₆ H ₃₆ N ₄ O ₂
294368	1-Me-2-pyrrolidinyl	2-thienyl	-(CH2)3-		C ₂₅ H ₃₆ N ₄ O ₂ S
294369	1-Me-2-pyrrolidinyl	2-thienyl	-(CH2)2-		C ₂₄ H ₃₄ N ₄ O ₂ S
294372	Ph	3-MeO-Ph	-CH2-		C ₂₇ H ₃₁ N ₃ O ₃
294373	2-pyrrolidinyl	Ph	-(CH2)3-	2HCl	C ₂₆ H ₃₆ N ₄ O ₂ ·2HCl
294374	2-thienyl	3-MeO-Ph	-CH2-		C ₂₅ H ₂₉ N ₃ O ₃ S
294375	1-Me-2-pyrrolidinyl	3-MeO-Ph	-CH2-		C ₂₆ H ₃₆ N ₄ O ₃
294376	1-Me-2-pyrrolidinyl	3-MeO-Ph	-(CH2)3-		C ₂₈ H ₄₀ N ₄ O ₃

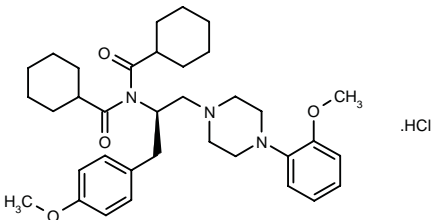
SOURCE – Sankyo.

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1. Naruto, S. et al. (Sankyo Co., Ltd.) *Therapeutic or preventive agents for psychoneurotic symptom*. JP 2000204040.

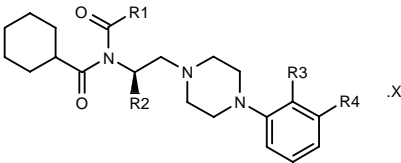
294546

N-(Cyclohexylcarbonyl)-*N*-[2-(4-methoxyphenyl)-1(*R*)-[4-(2-methoxyphenyl)piperazin-1-ylmethyl]ethyl]cyclohexanecarboxamide hydrochloride



C35 H49 N3 O4 . HCl; Mol wt: 612.2500

ACTION – Agent for the treatment of anxiety, depression, eating disorders, hypertension, emesis, schizophrenia, cognitive impairment in neurodegenerative diseases such as Alzheimer's disease and prostate cancer, a representative compound from a series of *N*-substituted imide derivatives acting as partial agonists and antagonists at 5-HT_{1A} receptors. *In vitro*, compound exhibited an IC₅₀ value of 0.38 nM for displacement of [³H]-8-OH-DPAT in CHO cells stably transfected with the human receptor. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	X	Formula
294547	cyclohexyl	H	OMe	H	2HCl	C ₂₇ H ₄₁ N ₃ O ₃ ·2HCl
294548	cyclohexyl	H	-CH=CHNH-		2HCl	C ₂₈ H ₄₀ N ₄ O ₂ ·2HCl
294549	cyclohexyl	H	-OCH2CH2O-		HCl H2O	C ₂₈ H ₄₁ N ₃ O ₄ ·HCl·H ₂ O
294550	cyclohexyl	Me	OMe	H	fumarate	C ₂₈ H ₄₃ N ₃ O ₃ ·C ₄ H ₄ O ₄
294551	cyclohexyl	1-Me-3-indolyl-CH2	OMe	H	HCl H2O	C ₃₇ H ₅₀ N ₄ O ₃ ·HCl·H ₂ O
294552	Ph	H	-OCH2CH2O-		HCl H2O	C ₂₈ H ₃₅ N ₃ O ₄ ·HCl·H ₂ O

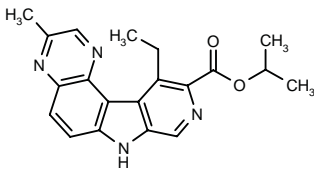
SOURCE – American Home Products.

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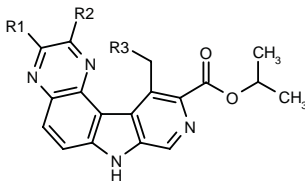
294863

11-Ethyl-3-methyl-7*H*-pyrido[4',3':4,5]pyrrolo[3,2-*f*]quinoxaline-10-carboxylic acid isopropyl ester

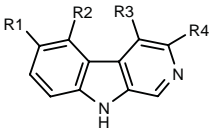


C20 H20 N4 O2; Mol wt: 348.4040

ACTION – Anxiolytic agent with high affinity for the benzodiazepine binding site and also useful for the treatment of memory and learning disorders. Other specifically claimed anellated β -carboline are:



Compound	R1	R2	R3	Formula
294864	H	Me	Me	C ₂₀ H ₂₀ N ₄ O ₂
294866	-(CH2)4-		OMe	C ₂₃ H ₂₄ N ₄ O ₃
294868	CH2OMe	H	OMe	C ₂₁ H ₂₂ N ₄ O ₄



Compound	R1,R2	R3	R4	Formula
294869	-CH=CHCH=CH-	CH2OMe	i-PrOCO	C ₂₁ H ₂₀ N ₂ O ₃
294871	-OC(Pr)=N-	Me	i-PrOCO	C ₂₀ H ₂₁ N ₃ O ₃
294872	-OC[CH(OH)CH2OH]=N-	CH2OMe	i-PrOCO	C ₂₀ H ₂₁ N ₃ O ₆
294875	-OC(i-Pr)=N-	CH2OMe	5-(MeOCH2)-3-isoxazolyI	C ₂₂ H ₂₂ N ₄ O ₄
294877	-SC(NH2)=N-	Et	i-PrOCO	C ₁₈ H ₁₈ N ₄ O ₂ S
294879	-SC(NH2)=N-	CH2OMe	i-PrOCO	C ₁₈ H ₁₈ N ₄ O ₃ S
294880	-NHC(CO2Et)=CH-	H	EtOCO	C ₁₉ H ₁₇ N ₃ O ₄
294881	-NHC(i-Pr)=N-	CH2OMe	i-PrOCO	C ₂₁ H ₂₄ N ₄ O ₃

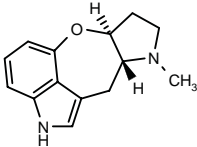
SOURCE – Schering AG.

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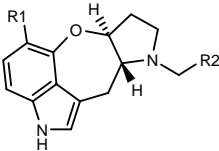
295264

(6a*S*,9a*R*)-9-Methyl-6a,7,8,9,9a,10-hexahydro-2*H*-pyrrolo[2',3':6,7]oxepino[4,3,2-*cd*]indole



C14 H16 N2 O; Mol wt: 228.2934

ACTION – Agent for the treatment of CNS disorders such as sleep disorders, anxiety, depression, schizophrenia, stroke, dementia, Parkinson’s disease and pain, with high affinity for 5-HT receptors such as 5-HT_{1A} (rat; K_i = 1.3 ± 0.4 nM) , 5-HT₂ (rat; K_i = 180 ± 46 nM), 5-HT₆ (rat; K_i = 0.38 ± 0.12 nM) and 5-HT₇ receptors (human; K_i = 2.5 ± 0.3 nM). Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	Formula
295265	t-Bu	H	C ₁₈ H ₂₄ N ₂ O
295266	H	Et	C ₁₈ H ₂₀ N ₂ O

SOURCE – Shionogi.

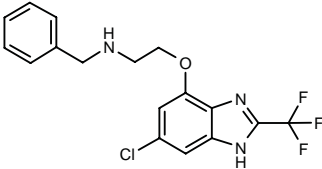
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1. Kamigauchi, T. and Yasui, M. (Shionogi & Co. Ltd.) *Heterocyclic cpds. having affinities for serotonin receptors*. WO 0059909.

ANTIPSYCHOTIC DRUGS

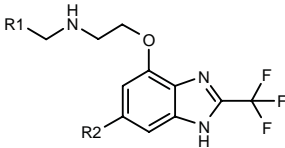
294854

N-Benzyl-*N*-[2-[6-chloro-2-(trifluoromethyl)-1*H*-benzimidazol-4-yloxy]ethyl]amine



C17 H15 Cl F3 N3 O; Mol wt: 369.7725

ACTION – Dopamine D2 receptor agonist with selectivity for dopamine autoreceptors, giving IC₅₀ values of 1.42 and 150.5 nM for displacement of [³H]-quinpirole and [³H]-spiroperidol binding, respectively. Potentially useful for the treatment of schizophrenia, Parkinson’s disease, Tourette’s syndrome and drug and alcohol addiction. Other specifically claimed 4-aminoalkoxy-1*H*-benzimidazoles include the following:



Compound	R1	Formula
294855	1-Naph	C ₂₁ H ₁₈ F ₃ N ₃ O
294856	4-Cl-Ph	C ₁₇ H ₁₄ Cl ₂ F ₃ N ₃ O
294857	4-F-Ph	C ₁₇ H ₁₅ F ₄ N ₃ O
294858	4-CF3-Ph	C ₁₈ H ₁₅ F ₆ N ₃ O

SOURCE – American Home Products.

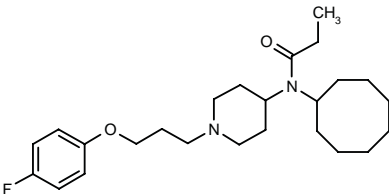
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AC-165024

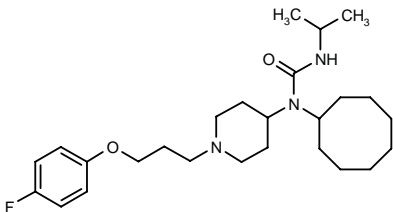
296394

N-Cyclooctyl-*N*-[1-[3-(4-fluorophenoxy)propyl]piperidin-4-yl]propanamide



C25 H39 F N2 O2; Mol wt: 418.5931

ACTION – 5-HT_{2A} receptor inverse agonist (pIC₅₀ = 7.9) and 5-HT_{2A} antagonist (IC₅₀ = 20 nM), a spiperone analogue with no significant inverse agonist activity at 5-HT_{2B} or 5-HT_{2C} receptors at up to 3000 nM and devoid of activity at muscarinic M₁, histamine H₁ and 5-HT_{1A} receptors. Potentially useful as an antipsychotic agent. Another spiperone analogue is:



AC-165043 [296395]: C26 H42 F N3 O2

SOURCE – Acadia.

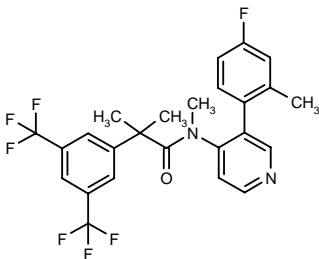
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TREATMENT OF MOOD DISORDERS

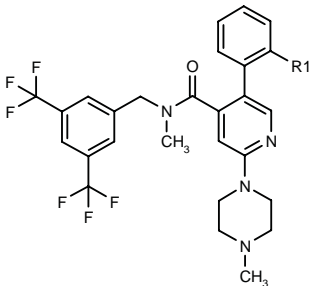
294256

2-[3,5-Bis(trifluoromethyl)phenyl]-N-[3-(4-fluoro-2-methyl-phenyl)pyridin-4-yl]-N-methylisobutyramide

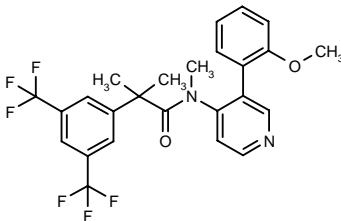


C25 H21 F7 N2 O; Mol wt: 498.4399

ACTION – Tachykinin NK₁ receptor antagonist for the treatment of CNS disorders, in particular depression and emesis. This compound demonstrated good affinity for NK₁ receptors in CHO cells expressing the human receptor (pK_i = 8.56). Other exemplified 3-phenylpyridine derivatives are:



Compound	R1	Formula
294257	OMe	C ₂₈ H ₂₈ F ₆ N ₄ O ₂
294259	Cl	C ₂₇ H ₂₆ ClF ₆ N ₄ O



294258: C25 H22 F6 N2 O2

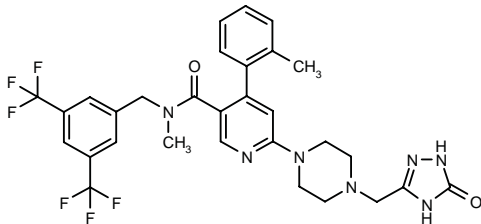
SOURCE – Roche.

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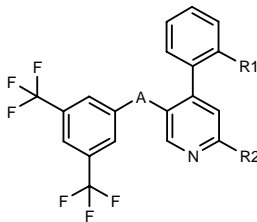
294283

N-[3,5-Bis(trifluoromethyl)benzyl]-N-methyl-4-(2-methyl-phenyl)-6-[4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl-methyl)piperazin-1-yl]pyridine-3-carboxamide



C30 H29 F6 N7 O2; Mol wt: 633.5941

ACTION – Tachykinin NK₁ receptor antagonist giving a pK_i of 9.64 in CHO cells expressing the human NK₁ receptor. Preferred indications for this compound include depressive disorders and emesis. Other compounds from this series of 4-phenylpyridine derivatives include the following:



Compound	R1	R2	A	Formula
294285	Cl	H	-CH2N(Me)CO-	C ₂₂ H ₁₅ ClF ₆ N ₂ O
294286	Me	H	-C(Me)2CON(Me)-	C ₂₅ H ₂₂ F ₆ N ₂ O
294288	Me	4-morpholinyl- -CH2CH2N(Me)	-C(Me)2CON(Me)-	C ₃₂ H ₃₆ F ₆ N ₄ O ₂
294290	Me	1-Piz	-C(Me)2CON(Me)-	C ₂₉ H ₃₀ F ₆ N ₄ O

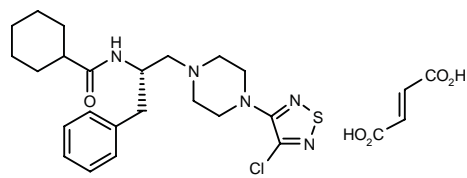
SOURCE – Roche.

REFERENCES

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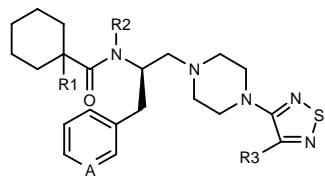
294540

N-[1 (S)-Benzyl-2-[4-(4-chloro-1,2,5-thiadiazol-3-yl)-piperazin-1-yl]ethyl]cyclohexanecarboxamide fumarate



C22 H30 Cl N5 O S . C4 H4 O4; Mol wt: 564.1036

ACTION – Serotonergic agent with high affinity and selectivity for the 5-HT_{1A} receptor, potentially useful for the treatment of depression and anxiety. This compound demonstrated the ability to displace [³H]-8-OH-DPAT binding in CHO cells transfected with the human 5-HT_{1A} receptor (K_i = 0.84 nM) and exhibited agonist activity when tested for reversal of cAMP stimulation in CHO cells transfected with the human 5-HT_{1A} receptor (E_{max} = 93%; EC₅₀ = 4.61 nM). Other exemplified diazole derivatives are:



Compound	R1	R2	R3	A	Formula
294541	H	Me	Cl	CH	C ₂₃ H ₃₂ ClN ₅ OS
294542	H	Me	OMe	CH	C ₂₄ H ₃₅ N ₅ O ₂ S
294543	Me	H	OMe	N	C ₂₃ H ₃₄ N ₆ O ₂ S

Some compounds of the invention, which showed no agonist activity in the cAMP test, were further evaluated and found to reverse agonist-induced activity.

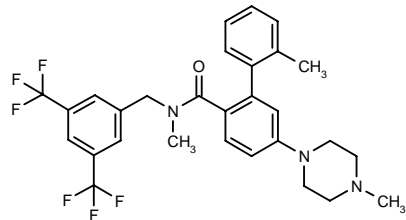
SOURCE – American Home Products.

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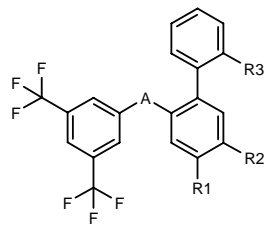
294781

N-[3,5-Bis(trifluoromethyl)benzyl]-N,2'-dimethyl-5-(4-methylpiperazin-1-yl)biphenyl-2-carboxamide



C29 H29 F6 N3 O; Mol wt: 549.5561

ACTION – Tachykinin NK₁ receptor antagonist with potential for the treatment of CNS disorders, in particular depression and emesis. It exhibited a pK_i value of 8.84 when evaluated in CHO cells expressing the human NK₁ receptor. Other specifically claimed biphenyl derivatives are:



Compound	R1	R2	R3	A	Formula
294782	H	4-Me-1-Piz	Cl	-CH2N(Me)CO-	C ₂₈ H ₂₆ ClF ₆ N ₃ O
294783	NO2	H	Me	-C(Me)2CON(Me)-	C ₂₆ H ₂₂ F ₆ N ₂ O ₃
294784	NH2	H	Me	-C(Me)2CON(Me)-	C ₂₆ H ₂₄ F ₆ N ₂ O
294785	NHMe	H	Me	-C(Me)2CON(Me)-	C ₂₇ H ₂₆ F ₆ N ₂ O
294786	H	H	Me	-C(Me)2CON(Me)-	C ₂₆ H ₂₃ F ₆ NO
294787	H	H	NH2	-C(Me)2CON(Me)-	C ₂₅ H ₂₂ F ₆ N ₂ O

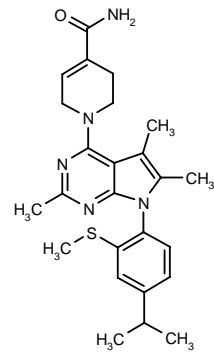
SOURCE – Roche.

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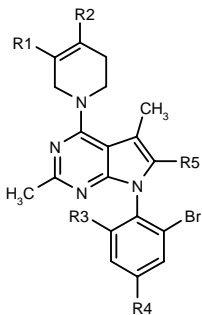
294834

1-[7-[4-Isopropyl-2-(methylsulfanyl)phenyl]-2,5,6-trimethyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide

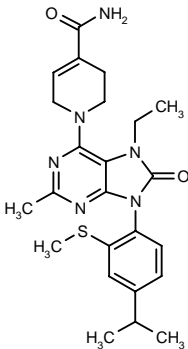


C25 H31 N5 O S; Mol wt: 449.6199

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist (IC₅₀ = 100 nM or less against [¹²⁵I]-CRF binding in rat frontal cortex membranes) with potential in the treatment of depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorders, hypertension, gastrointestinal disorders, drug dependence, cerebral infarction, ischemia and edema, head injury, inflammation and immune-related diseases. Other exemplified compounds from this series of carbamoyl tetrahydropyridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
294837	H	CONH2	Br	CF3	Me	C ₂₂ H ₂₀ Br ₂ F ₃ N ₅ O
294838	CONH2	H	Br	Br	Me	C ₂₁ H ₂₀ Br ₃ N ₅ O
294839	CONH2	H	OMe	Br	Me	C ₂₂ H ₂₃ Br ₂ N ₅ O ₂
294840	H	CONH2	SMe	Br	H	C ₂₁ H ₂₁ Br ₂ N ₅ OS
294841	CONH2	H	Me	Br	H	C ₂₁ H ₂₁ Br ₂ N ₅ O



294836: C₂₄ H₃₀ N₆ O₂ S

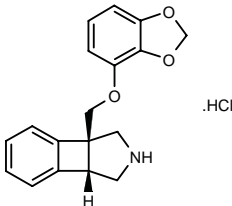
SOURCE – Taisho.

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294906

cis-3a-(1,3-Benzodioxol-4-yloxymethyl)-2,3,3a,7b-tetrahydro-1*H*-benzo[3,4]cyclobuta[1,2-*c*]pyrrole hydrochloride



C₁₈ H₁₇ N O₃ . HCl; Mol wt: 331.7972

ACTION – 5-HT reuptake inhibitor (pK_i = 7.9 for [³H]-paroxetine binding in rat frontal cortex preparations) with potential for the treatment of depression, panic attacks, obsessive–compulsive disorders, phobia, drug abuse and anxiety. When tested *in vivo* in rats, compound was shown to increase 5-HT, dopamine and noradrenaline levels in the brain by 226.3 ± 20.1%, 54.8 ± 6.4% and 96.4 ± 7.8%, respectively, at 10 mg/kg s.c.

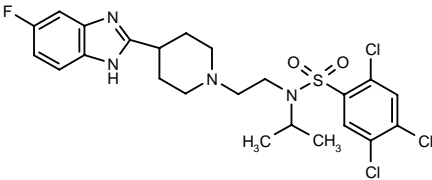
SOURCE – ADIR.

REFERENCES

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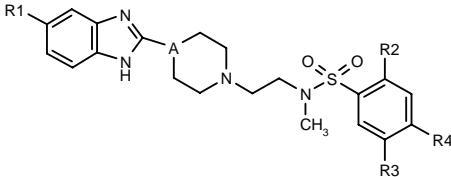
295251

2,4,5-Trichloro-*N*-[2-[4-(5-fluoro-1*H*-benzimidazol-2-yl)piperidin-1-yl]ethyl]-*N*-isopropylbenzenesulfonamide

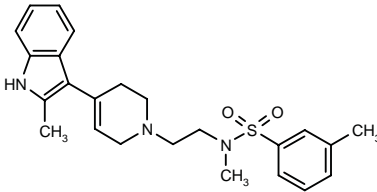


C₂₃ H₂₆ Cl₃ F N₄ O₂ S; Mol wt: 547.9074

ACTION – 5-HT₇ receptor antagonist, as demonstrated by inhibition of [³H]-5-carboxamidotryptamine binding to human receptors expressed in 293 cells (pK_i > 8.5). The compound is useful for the treatment of CNS disorders, in particular for the treatment or prevention of depression, migraine and sleep disorders. Other specifically claimed sulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
295252	H	H	Me	H	CH	C ₂₂ H ₂₈ N ₄ O ₂ S
295254	F	Br	Br	H	CH	C ₂₁ H ₂₃ Br ₂ FN ₄ O ₂ S
295255	F	Cl	H	F	CH	C ₂₁ H ₂₃ ClF ₂ N ₄ O ₂ S
295256	F	Cl	Cl	Cl	CH	C ₂₁ H ₂₂ Cl ₃ FN ₄ O ₂ S
295257	H	Cl	Me	Cl	N	C ₂₁ H ₂₅ Cl ₂ N ₅ O ₂ S



295253: C₂₄ H₂₉ N₃ O₂ S

SOURCE – GlaxoSmithKline.

REFERENCES

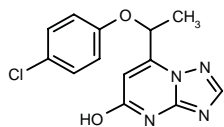
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

295239

7-[1-(4-Chlorophenoxy)ethyl][1,2,4]triazolo[1,5-*a*]pyrimidin-5-ol



C13 H11 Cl N4 O2; Mol wt: 290.7089

ACTION – Neuroprotective agent for the treatment of seizures, neurological disorders such as epilepsy and conditions where there is neurological damage such as stroke, brain trauma, head injuries and hemorrhage, proven to significantly increase the threshold for maximal electroshock-induced seizures in mice following both i.p. (77% increase) and p.o. (22% increase) administration at a dose of 100 mg/kg.

SOURCE – Knoll (Abbott).

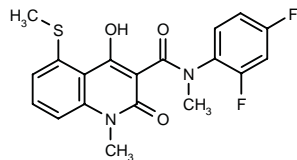
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THERAPY OF IMMUNOLOGIC
NEUROMUSCULAR DISORDERS

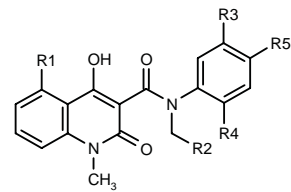
294352

N-(2,4-Difluorophenyl)-4-hydroxy-*N*,1-dimethyl-5-(methylsulfanyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide



C19 H16 F2 N2 O3 S; Mol wt: 390.4084

ACTION – Agent for the treatment of autoimmune diseases, in particular multiple sclerosis, shown to inhibit acute experimental autoimmune encephalomyelitis in mice by 28 and 49% at 0.04 and 0.2 mg/kg p.o., respectively. Roquinimex, used as control, showed more than 50% inhibition at > 5 mg/kg. In contrast to roquinimex, titel compound was found to be nonteratogenic in rats. Other specifically claimed quinoline derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
294353	SMe	Et	H	H	H	C ₂₁ H ₂₂ N ₂ O ₃ S
294354	SMe	H	H	H	CF ₃	C ₂₀ H ₁₇ F ₃ N ₂ O ₃ S
294355	SMe	H	F	F	H	C ₁₉ H ₁₆ F ₂ N ₂ O ₃ S
294356	SOMe	Et	H	H	H	C ₂₁ H ₂₂ N ₂ O ₄ S

SOURCE – Active Biotech.

REFERENCES

1. Bjork, A. et al. (Active Biotech AB) *Quinoline derivs*. US 6121287.

MAb 2C10

295243

Rat monoclonal antibody to interleukin-18

ACTION – Rat monoclonal antibody (MAb) specific for human IL-18, with potential in the treatment or diagnosis of IL-18-mediated disorders, particularly autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease and psoriasis. Compound exhibited a K_D value of 39 pM and was shown to inhibit hIL-18-induced interferon gamma production in human peripheral blood mononuclear cells (PBMCs) with an IC₅₀ value of 0.1 nM. Other exemplified compounds from this series of rodent anti-IL-18 antibodies include the following:

Rat monoclonal antibody to interleukin-18

MAb 14B7 [295244]

Murine monoclonal antibody to interleukin-18

MAb 13G9 [295245]

SOURCE – GlaxoSmithKline.

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TIPLIMOTIDE

Prop INN

263143

[D-Ala⁸³,L-Lys⁸⁴,L-Leu⁸⁹,L-Ala⁹¹]-myelin basic protein-(83-99)

D-Alanyl-L-lysyl-L-prolyl-L-valyl-L-valyl-L-histidyl-L-leucyl-L-phenylalanyl-L-alanyl-L-asparaginyl-L-isoleucyl-L-valyl-L-threonyl-L-prolyl-L-arginyl-L-threonyl-L-proline

CGP-77116
MSP-771A
NBI-5788

C87 H143 N25 O20; Mol wt: 1859.2420

ACTION – Vaccine for the treatment of multiple sclerosis (MS), an altered peptide ligand (APL) designed from the immunodominant region (83-99) of the neuroantigen myelin basic protein (MBP), proven to reduce disease severity and progression for extended periods in pre-clinical models of MS. Phase II clinical studies in patients with relapsing–remitting MS demonstrated that it was safe and well tolerated at all dose levels (5, 25 and 50 mg), and 50% of the patients who completed the double-blind phase of the study in the low-dose group (5 mg) experienced greater reductions in new lesions and a reduction in total lesion load and volume as compared with the placebo group.

SOURCE – Neurocrine Biosciences.

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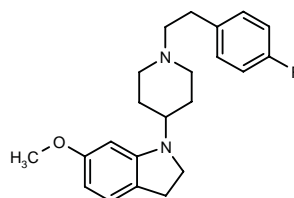
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ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

ER-41114

296948

1-[1-[2-(4-Fluorophenyl)ethyl]piperidin-4-yl]-6-methoxy-2,3-dihydro-1H-indole



C22 H27 F N2 O; Mol wt: 354.4663

ACTION – Dual 5-HT_{1A} and 5-HT₂ receptor antagonist with respective K_i values of 1.1 and 4.1 nM, and selectivity relative to α_1 -adrenoceptors and dopamine D2 receptors (K_i = 71.3 and 156.7 nM, respectively). *In vivo*, compound showed muscle relaxant activity in the Straub tail test following i.p. doses (3 mg/kg) devoid of central side effects such as anesthesia. Potentially useful as a central muscle relaxant.

SOURCE – Eisai.

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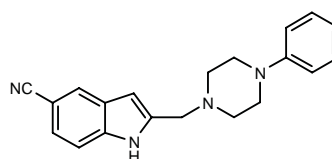
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TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

FAUC-299

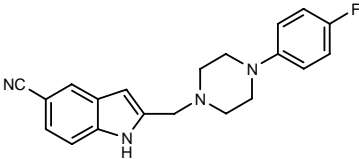
296689

2-(4-Phenylpiperazin-1-ylmethyl)-1H-indole-5-carbonitrile



C20 H20 N4; Mol wt: 316.4060

ACTION – High-affinity dopamine D4 receptor ligand (K_i = 0.52 nM against human D4.4 receptors) with very high selectivity over other dopamine receptor subtypes including bovine D1, human D2long, human D2short and human D3 (K_i = 13,000, 3100, 290 and 1700 nM, respectively). In *in vitro* functional mitogenesis assays in CHO10001 cells stably expressing the human D4.2 receptor, compound exhibited partial agonist activity, with an EC_{50} of 1.5 nM and an efficacy 35% that of the full D4 agonist quinpirole. Potentially useful for the treatment of neuropsychiatric disorders such as attention deficit hyperactivity disorder, mood disorders or Parkinson’s disease. Another selected compound from this series of cyanoindole derivatives is:



FAUC-316 [296690]: C20 H19 F N4

SOURCE – Friedrich-Alexander-Universität, Erlangen (DE).

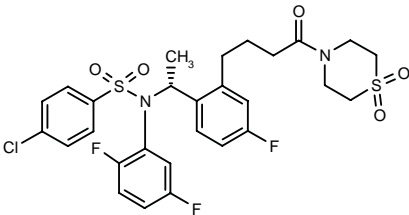
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TREATMENT OF DISORDERS OF COGNITION

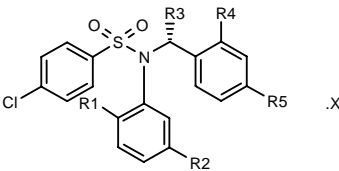
294272

4-Chloro-*N*-(2,5-difluorophenyl)-*N*-[1(*R*)-[2-[4-(1,1-dioxothiomorpholin-4-yl)-4-oxobutyl]-4-fluorophenyl]-ethyl]benzenesulfonamide



C28 H28 Cl F3 N2 O5 S2; Mol wt: 629.1172

ACTION – Modulator of the production of β -amyloid protein, useful for the treatment of CNS disorders related to the accumulation of β -amyloid in the cerebral extracellular perivascular space, in particular Alzheimer’s disease. The compound inhibited β -amyloid production in human neuroglioma H4 cells expressing amyloid precursor protein (IC_{50} = 25 nM or less). Other exemplified sulfonamide compounds are:



Compound	R1=R2	R3	R4	R5	X	Formula
294273	F	H	1-Pip-(CH2)3O	H	HCl	C ₂₇ H ₂₉ ClF ₂ N ₂ O ₃ S.HCl
294274	F	Me	(CH2)4SO2NHMe	F		C ₂₅ H ₂₆ ClF ₃ N ₂ O ₄ S ₂
294275	F	Me	t-BuONHCO(CH2)3	F		C ₂₈ H ₃₀ ClF ₃ N ₂ O ₄ S
294278	F	Me	1-imidazolyl-(CH2)3	F	HCl	C ₂₆ H ₂₃ ClF ₃ N ₃ O ₂ S.HCl
294280	F	Me	1-Pip-(CH2)3O	H	HCl	C ₂₈ H ₃₁ ClF ₂ N ₂ O ₃ S.HCl
294282	F	Me	1-tetrazolyl-(CH2)3	H		C ₂₄ H ₂₂ ClF ₂ N ₅ O ₂ S
294284	F	Me	CH2CH2SO2-CH2CH2CO2H	F		C ₂₅ H ₂₃ ClF ₃ N ₂ O ₆ S ₂
294287	Cl	H	1-Pip-(CH2)3O	H		C ₂₇ H ₂₉ Cl ₂ N ₂ O ₃ S
294289	F	Me	1,3-benzodioxol-5-yl-CH2NHCOCH2CH2	F		C ₃₁ H ₂₆ ClF ₃ N ₂ O ₅ S
294291	F	Me	1-tetrazolyl-CH2CH2	H		C ₂₃ H ₂₀ ClF ₂ N ₅ O ₂ S

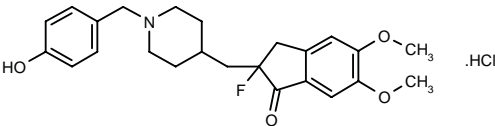
SOURCES – Bristol-Myers Squibb; Merck & Co.

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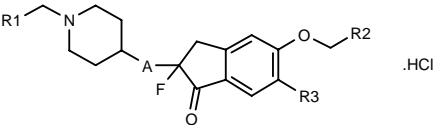
294398¹

2-Fluoro-2-[1-(4-hydroxybenzyl)piperidin-4-ylmethyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one hydrochloride



C24 H28 F N O4 . HCl; Mol wt: 449.9471

ACTION – Acetylcholinesterase inhibitor with an IC_{50} of 0.32 nM versus 6.7 nM for donepezil. Potentially useful for the treatment of Alzheimer’s disease, senile dementia and attention deficit hyperactivity disorder. Other exemplified fluorides of 4-substituted piperidine derivatives are:



Compound	R1	R2	R3	A	Formula
294399 ¹	Ph	Me	OEt	-CH2-	C ₂₆ H ₃₂ FNO ₃ .HCl
294400 ^{1,2}	3-F-Ph	H	OMe	-CH2-	C ₂₄ H ₂₇ F ₂ NO ₃ .HCl
294401 ¹	3-Me-Ph	H	OMe	-CH2-	C ₂₅ H ₃₀ FNO ₃ .HCl
294403 ¹	cyclohexyl	H	OMe	-CH2-	C ₂₄ H ₃₄ FNO ₃ .HCl
294409 ¹	3-NO2-Ph	H	OMe	-CH2-	C ₂₄ H ₂₇ FN ₂ O ₅ .HCl
294410 ¹	Ph	H	H	-CH2-	C ₂₃ H ₂₆ FNO ₂ .HCl
294411 ¹	Ph	H	OMe	-(CH2)3-	C ₂₆ H ₃₂ FNO ₃ .HCl
294412 ¹	Ph	Et	OPr	-CH2-	C ₂₈ H ₃₆ FNO ₃ .HCl

SOURCE – Eisai.

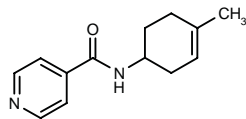
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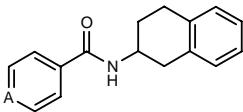
294505

N-(4-Methyl-3-cyclohexen-1-yl)pyridine-4-carboxamide

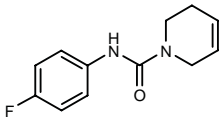


C13 H16 N2 O; Mol wt: 216.2824

ACTION – Cholinergic activity potentiator proven to induce penile erections in rats (0.71 erections/h at 0.1 mg/kg i.p.). The compound is useful for the treatment of amnesia and dementia. Other exemplified amide compounds are:



Compound	A	Formula
294507	C(F)	C ₁₇ H ₁₆ FNO
294508	N	C ₁₆ H ₁₆ N ₂ O



294506: C12 H13 F N2 O

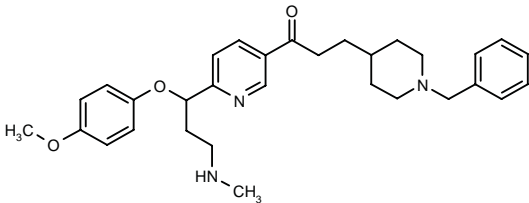
SOURCE – Fujisawa.

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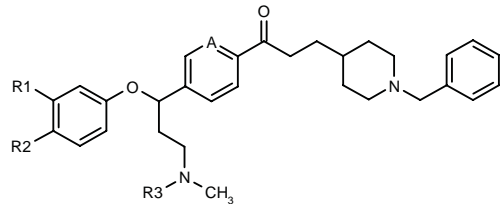
294663

3-(1-Benzylpiperidin-4-yl)-1-[6-[1-(4-methoxyphenoxy)-3-(methylamino)propyl]pyridin-3-yl]propan-1-one



C31 H39 N3 O3; Mol wt: 501.6671

ACTION – Dual-action compound that inhibits acetylcholinesterase (IC₅₀ = 0.4 nM) and 5-HT reuptake, as demonstrated by inhibition of the accumulation of tritiated 5-HT in rat whole brain synaptosomes (IC₅₀ = 23 nM). Potentially useful for the treatment of Alzheimer's disease, depression, Huntington's chorea, tardive dyskinesia, and obsessive and panic disorders. Other exemplified compounds are:



Compound	R1	R2	R3	A	Formula
294664	H	OMe	H	CH	C ₃₂ H ₄₀ N ₂ O ₃
294665	H	Cl	H	CH	C ₃₁ H ₃₇ ClN ₂ O ₂
294666	OMe	H	H	CH	C ₃₂ H ₄₀ N ₂ O ₃
294667	H	H	Me	CH	C ₃₂ H ₄₀ N ₂ O ₂
294668	H	OMe	Me	CH	C ₃₃ H ₄₂ N ₂ O ₃
294669	H	OMe	H	N	C ₃₁ H ₃₉ N ₃ O ₃

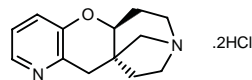
SOURCE – Sankyo.

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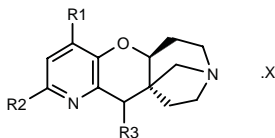
294717

trans-5a,6,7,8,9,10,10a,11-Octahydro-8,10a-methanopyrido[2',3':5,6]pyrano[2,3-*d*]azepine dihydrochloride



C13 H16 N2 O . 2HCl; Mol wt: 289.2042

ACTION – Agent with selective affinity for the $\alpha 4\beta 2$ subunit of nicotinic acetylcholine receptors, expected to be useful in the treatment of nicotinic receptor dysfunction of the CNS or the gastrointestinal system, i.e., cognition disorders, Parkinson's disease and other neurological diseases, withdrawal from tobacco and other addictive substances, pain, cerebrovascular diseases, psychiatric pathologies and inflammatory gastrointestinal diseases. Other exemplified pyridopyranoazepine compounds are:



Compound	R1	R2	R3	X	Isomer	Formula
294718	H	H	H	2HCl	5aS,10aR	C ₁₃ H ₁₆ N ₂ O.2HCl
294719	H	Br	H		trans	C ₁₃ H ₁₅ BrN ₂ O
294720	H	Br	H	HBr	(-)-trans	C ₁₃ H ₁₅ BrN ₂ O.HBr
294721	H	Cl	H	2HCl	(-)-trans	C ₁₃ H ₁₅ ClN ₂ O.2HCl
294722	H	CN	H	HBr	trans	C ₁₄ H ₁₅ N ₃ O.HBr
294723	H	4-Me-Ph	H	2HBr	trans	C ₂₀ H ₂₂ N ₂ O.2HBr
294724	H	H	Me	2HCl	trans	C ₁₄ H ₁₈ N ₂ O.2HCl
294725	H	H	2-furyl- -CH(OH)	2HBr	trans	C ₁₈ H ₂₀ N ₂ O ₃ .2HBr
294726	Br	Br	H	HBr	trans	C ₁₃ H ₁₄ Br ₂ N ₂ O.HBr

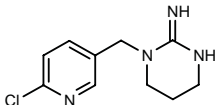
SOURCE – Sanofi-Synthélabo.

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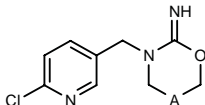
294817

1-(6-Chloropyridin-3-ylmethyl)hexahydropyrimidin-2-imine



C10 H13 Cl N4; Mol wt: 224.6937

ACTION – Nicotinic acetylcholine receptor (nAChR) agonist that binds with high affinity and selectivity to the $\alpha 4\beta 2$ receptor subtype versus the $\alpha 4\beta 1\gamma\delta$ subtype (K_i = 0.25 nM and 7.02 μ M, respectively). Agonist activity was demonstrated in functional assays in *Xenopus* oocytes, where compound elicited inward currents with an EC₅₀ value of 0.5 μ M. Potentially useful for the treatment of CNS disorders such as Alzheimer’s disease and other types of dementia, Parkinson’s disease, Down’s syndrome, Tourette’s syndrome, head injury, anxiety, depression, schizophrenia and pain. Other exemplified heterocyclic compounds include the following:



Compound	A	Formula
294818	-CH2-	C ₁₀ H ₁₂ ClN ₃ O
294819	bond	C ₉ H ₁₀ ClN ₃ O

SOURCE – Suntory.

REFERENCES

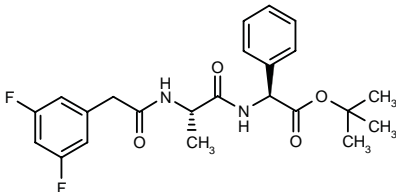
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AN-37124

295322

N-[2-(3,5-Difluorophenyl)acetyl]-L-alanyl-L-(2-phenyl)-glycine *tert*-butyl ester

DAPT
LY-374973



C23 H26 F2 N2 O4; Mol wt: 432.4644

ACTION – Orally active small-molecule inhibitor of γ -secretase, proven to inhibit β -amyloid production. Potentially useful for the treatment of Alzheimer’s disease.

SOURCES – Elan; Lilly.

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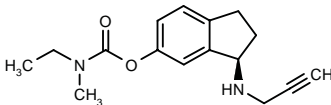
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TV-3326

269186

N-Ethyl-*N*-methylcarbamic acid 3(*R*)-(2-propynylamino)-2,3-dihydro-1*H*-inden-5-yl ester

TV-3219 (racemate)



C16 H20 N2 O2; Mol wt: 272.3460

ACTION – Neuroprotective agent for the treatment of Alzheimer’s disease, an inhibitor of cholinesterases (IC₅₀ = 51 and 1.7 μ M, respectively, for inhibition of acetylcholinesterase and butyrylcholinesterase) and of monoamine oxidase (MAO). It improves both cholinergic and aminergic transmission and decreases the formation of oxidative free radicals. Chronic oral administration at doses of 50-75 μ mol/kg led to selective inhibition of both brain MAO-A and MAO-B, with little or no effect on enzymes in liver and small intestine. Compound exhibited antidepressant-like activity in the mouse forced swimming test and attenuated the memory impairment induced by scopolamine in the Morris water maze at doses ranging from 35 to 100 μ mol/kg. In addition, it exhibited neuro-protective activity both *in vitro* in PC12 cells and *in vivo* in

models of global cerebral ischemia in gerbils and edema in mice. In gerbils, compound given at a dose of 75 µmol/kg i.p. 2 h before and 2 and 24 h after bilateral carotid artery occlusion significantly reduced hippocampal cell damage, and in mice it reduced cerebral edema by 50% and accelerated the time to recovery from motor deficits and spatial memory impairment when given at a dose of 75 µmol/kg s.c. 5 min after closed-head injury.

SOURCES – Hebrew University, Jerusalem (IL); Teva.

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5. Youdim, M.B.H. et al. *MAO-A and novel cholinesterase-MAO inhibitors in the treatment of depression co-morbid to Parkinson's and Alzheimer's disease.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst S.06.6.

6. Youdim, M.B.H. et al. *Novel drugs possessing both cholinesterase and monoamine oxidase inhibitory activities.* Neurosci Lett 1999, (Suppl. 54): S45.

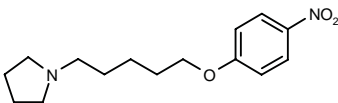
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8. Teva Pharmaceutical Industries Ltd. Annual Report 1997.

UCL-1972*,1-3

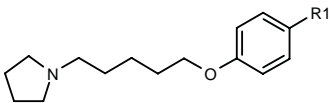
285642

1-[5-(4-Nitrophenoxy)pentyl]pyrrolidine



C15 H22 N2 O3; Mol wt: 278.3498

ACTION – Potent, nonimidazole histamine H₃ receptor antagonist, potentially useful for the treatment of memory and learning deficits, Alzheimer's disease, epilepsy, schizophrenia, sleep disturbances and obesity. Compound was active in inhibiting [³H]-histamine release from rat cerebral cortical synaptosomes (K_i = 39 nM) and in increasing *tele*-methylhistamine brain levels in mice after oral administration (ED₅₀ = 1.1 mg/kg). Other related H₃ antagonists include the following:



Compound	R1	Formula
296499 ^{1,3}	Ac	C ₁₇ H ₂₆ NO ₂
296500 ¹⁻³	H	C ₁₅ H ₂₃ NO

SOURCES – Bioprojet; INSERM, Paris Cedex (FR).

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2. Ganellin, C. et al. *Synthesis of potent non-imidazole histamine H₃-receptor antagonists.* Arch Pharm 1998, 331(12): 395.

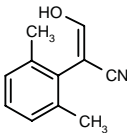
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*Identified compound **285642** (see **285641**) Drug Data Rep 2000, 022(05): 0411.

TREATMENT OF
CEREBROVASCULAR DISEASES

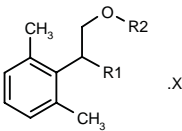
294057

2-(2,6-Dimethylphenyl)-3-hydroxy-2-propenenitrile



C11 H11 N O; Mol wt: 173.2139

ACTION – Sodium channel blocker, potentially useful in the treatment of epilepsy, hypoglycemia, hypoxia, anoxia, cerebral ischemia, stroke and neurodegenerative disorders, among others. Other exemplified substituted 3-phenoxy and 3-phenylalkoxy-2-phenyl-propylamines are:



Compound	R1	R2	X	Formula
294058	CN	H		C ₁₁ H ₁₃ NO
294060	CH2NH2	H	L-tartrate	C ₁₁ H ₁₇ NO .C ₄ H ₆ O ₆
294061	t-BuOCONHCH2	2,6-(F)2-PhCH2		C ₂₃ H ₂₉ F ₂ NO ₃
294062	allyl-NHCH2	2,6-(F)2-PhCH2	HBr	C ₂₁ H ₂₅ F ₂ NO.HBr
294063	CH2NHCH2Ph	2,6-(F)2-PhCH2	HCl	C ₂₅ H ₂₇ F ₂ NO.HCl
294067	1-Pip-CH2	2,6-(F)2-PhCH2	HCl	C ₂₃ H ₂₉ F ₂ NO.HCl
294068	1-Pip-CH2	2-F-PhCH2CH2	HCl	C ₂₄ H ₃₂ FNO.HCl

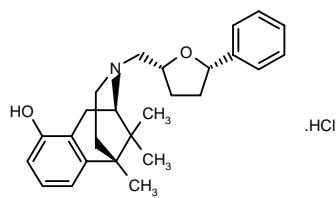
SOURCE – Boehringer Ingelheim.

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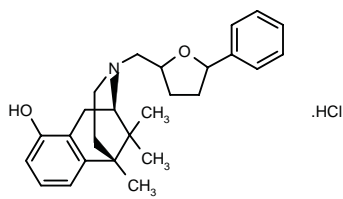
294087

(2*R*,6*S*)-6,11,11-Trimethyl-3-[5(*S*)-phenyltetrahydrofuran-2(*R*)-ylmethyl]-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ol hydrochloride



C26 H33 N O2 . HCl; Mol wt: 428.0126

ACTION – Sodium channel blocker potentially useful in the treatment of epilepsy, hypoglycemia, hypoxia, anoxia, cerebral ischemia, stroke and neurodegenerative disorders. Other exemplified substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ols are:



Compound	Isomer	Formula
294091	2 <i>R</i> ,3(2 <i>S</i> ,5 <i>S</i>),6 <i>S</i>	C ₂₆ H ₃₃ NO ₂ .HCl
294092	2 <i>R</i> ,3(2 <i>R</i> ,5 <i>R</i>),6 <i>S</i>	C ₂₆ H ₃₃ NO ₂ .HCl
294094	2 <i>R</i> ,3(2 <i>S</i> ,5 <i>R</i>),6 <i>S</i>	C ₂₆ H ₃₃ NO ₂ .HCl
294095	2 <i>RS</i> ,3(2 <i>S</i> ,5 <i>S</i>),6 <i>SR</i>	C ₂₆ H ₃₃ NO ₂ .HCl

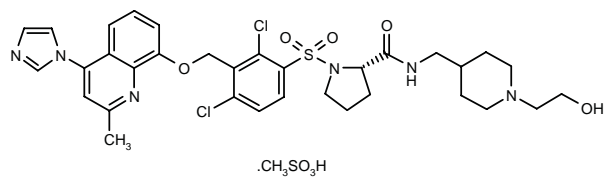
SOURCE – Boehringer Ingelheim.

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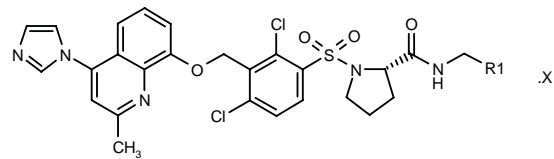
294200

1-[2,4-Dichloro-3-[4-(1 *H*-imidazol-1-yl)-2-methylquinolin-8-yloxymethyl]phenylsulfonyl]- *N*-[1-(2-hydroxyethyl)-piperidin-4-ylmethyl]-*L*-prolinamide methanesulfonate



C33 H38 Cl2 N6 O5 S . C H4 O3 S; Mol wt: 797.7778

ACTION – Bradykinin B₂ receptor antagonist with high affinity for this receptor (K_i = 0.034 nM) and potent antagonist activity (pA₂ = 9.3) in *in vitro* assays. This compound is useful for the treatment of painful and inflammatory conditions, in particular traumatic brain injury. Other exemplified heterocyclic benzenesulfonamide derivatives are:



Compound	R1	X	Formula
294201	4-[NH2C(=NH)]-Ph-CONHCH2CH2		C ₃₆ H ₃₆ Cl ₂ N ₈ O ₅ S
294202	1-[HO(CH2)3]-4-Pip	L-tartrate	C ₃₄ H ₄₀ Cl ₂ N ₆ O ₅ S.C ₄ H ₆ O ₆
294203	1-[HO(CH2)4]-4-Pip	L-tartrate	C ₃₅ H ₄₂ Cl ₂ N ₆ O ₅ S.C ₄ H ₆ O ₆

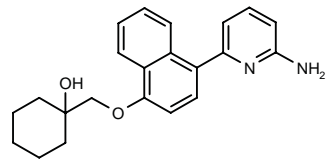
SOURCE – Fournier.

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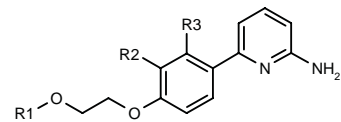
294262

1-[4-(6-Aminopyridin-2-yl)naphthalen-1-yloxymethyl]-cyclohexanol



C22 H24 N2 O2; Mol wt: 348.4436

ACTION – Nitric oxide synthase (NOS) inhibitor, potentially useful for the treatment of a variety of diseases including CNS and inflammatory disorders, septic shock and obesity. Other specifically claimed 2-aminopyridine derivatives are:



Compound	R1	R2	R3	Formula
294264	CH2CH2N(Me)2	-CH=CHCH=CH-		C ₂₁ H ₂₅ N ₃ O ₂
294265	H	-(CH2)4-		C ₁₇ H ₂₀ N ₂ O ₂
294266	CH2CH2N(Et)2	-CH=CHCH=CH-		C ₂₃ H ₂₉ N ₃ O ₂
294267	CH2CH2N(Pr)2	-CH=CHCH=CH-		C ₂₅ H ₃₃ N ₃ O ₂
294268	CH2CH2N(Me)CH2Ph	-CH=CHCH=CH-		C ₂₇ H ₂₉ N ₃ O ₂
294269	1-Pip-CH2CH2	-CH=CHCH=CH-		C ₂₄ H ₂₉ N ₃ O ₂
294270	4-Me-1-Piz-CH2CH2	-CH=CHCH=CH-		C ₂₄ H ₃₀ N ₄ O ₂
294271	6-NH2-3-aza-bicyclo[3.1.0]hexan-3-yl	-CH=CHCH=CH-		C ₂₄ H ₂₈ N ₄ O ₂

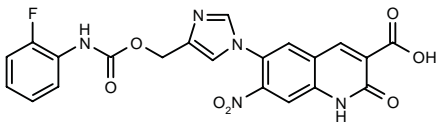
SOURCE – Pfizer.

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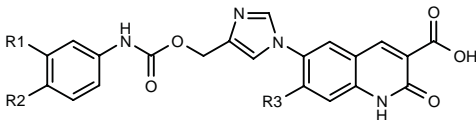
294377

6-[4-[N-(2-Fluorophenyl)carbamoyloxymethyl]-1*H*-imidazol-1-yl]-7-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid



C21 H14 F N5 O7; Mol wt: 467.3676

ACTION – Excitatory amino acid antagonist, particularly active at AMPA receptors, giving a K_i value of 8.22 nM when tested for binding affinity for AMPA receptors using rat cerebral cortex synaptosome preparations. Potentially useful for the treatment of cerebrovascular disorders. Other exemplified 6-substituted heteroquinoline carboxylic acid derivatives are:



Compound	R1	R2	R3	Formula
294378	H	H	NO2	C ₂₁ H ₁₅ N ₅ O ₇
294379	CO2H	H	NO2	C ₂₂ H ₁₅ N ₅ O ₉
294380	H	CO2H	NO2	C ₂₂ H ₁₅ N ₅ O ₉
294381	H	CO2H	CF3	C ₂₃ H ₁₅ F ₃ N ₄ O ₇

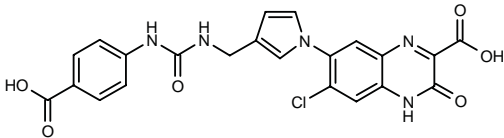
SOURCE – Kyorin.

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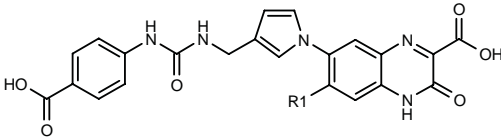
294383

7-[3-[3-(4-Carboxyphenyl)ureidomethyl]-1*H*-pyrrol-1-yl]-6-chloro-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid



C22 H16 Cl N5 O6; Mol wt: 481.8504

ACTION – Excitatory amino acid antagonist, particularly active at AMPA receptors, giving a K_i value of 0.067 μ M when tested for binding affinity for AMPA receptors using rat cerebral cortex synaptosome preparations. Potentially useful for the treatment of cerebrovascular disorders. Other exemplified 6-substituted-7-heteroquinoxaline carboxylic acid derivatives are:



Compound	R1	Formula
294386	OMe	C ₂₃ H ₁₉ N ₅ O ₇
294388	Me	C ₂₃ H ₁₉ N ₅ O ₆
294389	F	C ₂₂ H ₁₆ FN ₅ O ₆

SOURCE – Kyorin.

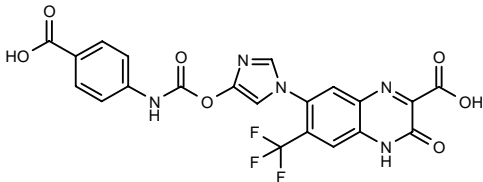
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GRA-334

296944

7-[4-(4-Carboxyphenylcarbamoyloxy)imidazol-1-yl]-3-oxo-6-(trifluoromethyl)-3,4-dihydroquinoxaline-2-carboxylic acid



C21 H12 F3 N5 O7; Mol wt: 503.3478

ACTION – Potent, selective and water-soluble glutamate AMPA receptor antagonist (K_i = 15.8 nM) with potent neuroprotective activity in a rat focal ischemia model. Potentially useful for the treatment of neurodegenerative disorders such as stroke, epilepsy, head trauma and Alzheimer's disease.

SOURCE – Kyorin.

REFERENCES

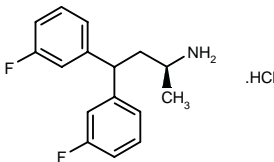
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NPS-1407.HCl

296292

(–)-4,4-Bis(3-fluorophenyl)butan-2(*S*)-amine hydrochloride

NPS-1408.HCl ([*R*]-isomer)



C16 H17 F2 N . HCl; Mol wt: 297.7742

ACTION – Potent, stereoselective NMDA receptor antagonist with an IC₅₀ of 89 nM, which is at least 10-fold lower than that of its enantiomer, for inhibition of NMDA/glycine-induced increases in cytosolic calcium in cultured rat cerebellar granule cells. *In vivo*, compound protected against brain injury induced by middle cerebral artery occlusion in a model of temporary focal ischemia in mice, giving a 37% reduction (compared to controls) in cerebral infarction at a dose of 2 mg/kg i.p. Moreover, it exhibited anticonvulsant activity in a mouse model of audiogenic seizures, with ED₅₀ values of 2.7 and 7.3 mg/kg after i.p. or p.o. administration, respectively. Potentially useful for the treatment of various neurological disorders including ischemic stroke, epilepsy and pain, as well as neurodegenerative disorders such as Parkinson’s disease.

SOURCE – NPS Pharmaceuticals.

REFERENCES

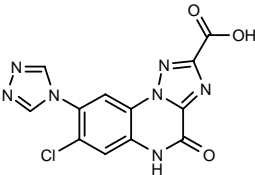
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TQX-173

295000

7-Chloro-4-oxo-8-(4*H*-1,2,4-triazol-4-yl)-4,5-dihydro-[1,2,4]triazolo[1,5-*a*]quinoxaline-2-carboxylic acid



C12 H6 Cl N7 O3; Mol wt: 331.6784

ACTION – Potent glutamate AMPA receptor antagonist with submicromolar binding affinity for rat AMPA receptors (K_i = 0.14 μM) and high selectivity versus glycine and kainate receptors (K_i = 33.5 and 11.6 μM, respectively). In electrophysiological studies using mouse cortical wedge preparations, compound was shown to competitively antagonize AMPA-induced depolarization (IC₅₀ = 2.3 μM) and was at least 20-fold less potent in blocking NMDA-evoked responses (IC₅₀ = 46 μM).

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

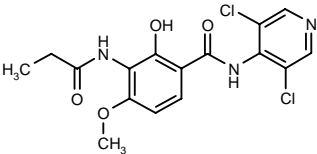
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RESPIRATORY DRUGS

ASTHMA THERAPY

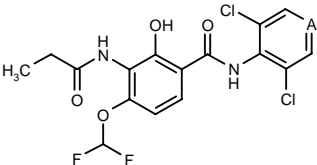
294047

N-(3,5-Dichloropyridin-4-yl)-2-hydroxy-4-methoxy-3-(propionamido)benzamide



C16 H15 Cl2 N3 O4; Mol wt: 384.2175

ACTION – Phosphodiesterase type 4 (PDE4) and TNF production inhibitor with potential in the treatment of a variety of inflammatory and autoimmune diseases, particularly asthma, chronic obstructive pulmonary disease and chronic bronchitis. Other specifically claimed compounds from this series of amino(thio)phenols are:



Compound	A	Formula
294050	N	C ₁₆ H ₁₃ Cl ₂ F ₂ N ₃ O ₄
294052	N(O)	C ₁₆ H ₁₃ Cl ₂ F ₂ N ₃ O ₅

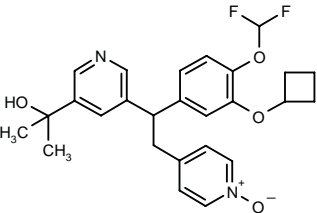
SOURCE – Darwin Discovery.

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1. Sharpe, A. and Kendall, H.J. (Darwin Discovery Ltd.) *Amino(thio)phenols and their therapeutic use*. WO 0048998.

294224

2-[5-[1-[3-(Cyclobutyloxy)-4-(difluoromethoxy)phenyl]-2-(1-oxido-4-pyridinyl)ethyl]-3-pyridinyl]-2-propanol



C26 H28 F2 N2 O4; Mol wt: 470.5132

ACTION – Antiinflammatory agent, a phosphodiesterase type 4 (PDE4) inhibitor for the treatment of inflammatory airways disorders such as asthma. Another specifically claimed compound is:

ACTION – Potent, stereoselective NMDA receptor antagonist with an IC₅₀ of 89 nM, which is at least 10-fold lower than that of its enantiomer, for inhibition of NMDA/glycine-induced increases in cytosolic calcium in cultured rat cerebellar granule cells. *In vivo*, compound protected against brain injury induced by middle cerebral artery occlusion in a model of temporary focal ischemia in mice, giving a 37% reduction (compared to controls) in cerebral infarction at a dose of 2 mg/kg i.p. Moreover, it exhibited anticonvulsant activity in a mouse model of audiogenic seizures, with ED₅₀ values of 2.7 and 7.3 mg/kg after i.p. or p.o. administration, respectively. Potentially useful for the treatment of various neurological disorders including ischemic stroke, epilepsy and pain, as well as neurodegenerative disorders such as Parkinson’s disease.

SOURCE – NPS Pharmaceuticals.

REFERENCES

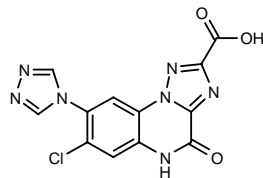
1. Mueller, A.L. et al. (NPS Pharmaceuticals, Inc.) *Cpds. active at a novel site on receptor-operated calcium channels useful for treatment of neurological disorders and diseases*. US 6071970.

2. Moe, S.T. et al. *Chiral synthesis and pharmacological evaluation of NPS 1407: A potent, stereoselective NMDA receptor antagonist*. Bioorg Med Chem Lett 2000, 10(21): 2411.

TQX-173

295000

7-Chloro-4-oxo-8-(4*H*-1,2,4-triazol-4-yl)-4,5-dihydro-[1,2,4]triazolo[1,5-*a*]quinoxaline-2-carboxylic acid



C12 H6 Cl N7 O3; Mol wt: 331.6784

ACTION – Potent glutamate AMPA receptor antagonist with submicromolar binding affinity for rat AMPA receptors (K_i = 0.14 μM) and high selectivity versus glycine and kainate receptors (K_i = 33.5 and 11.6 μM, respectively). In electrophysiological studies using mouse cortical wedge preparations, compound was shown to competitively antagonize AMPA-induced depolarization (IC₅₀ = 2.3 μM) and was at least 20-fold less potent in blocking NMDA-evoked responses (IC₅₀ = 46 μM).

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

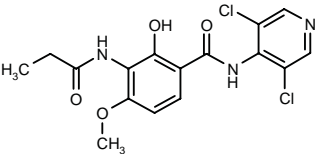
1. Catarzi, D. et al. *7-Chloro-4,5-dihydro-8-(1,2,4-triazol-4-yl)-4-oxo-1,2,4-triazolo-[1,5-*a*]quinoxaline-2-carboxylates as novel highly selective AMPA receptor antagonists*. J Med Chem 2000, 43(21): 3824.

RESPIRATORY DRUGS

ASTHMA THERAPY

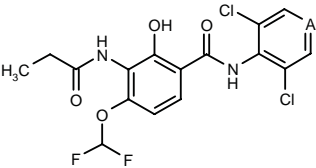
294047

N-(3,5-Dichloropyridin-4-yl)-2-hydroxy-4-methoxy-3-(propionamido)benzamide



C16 H15 Cl2 N3 O4; Mol wt: 384.2175

ACTION – Phosphodiesterase type 4 (PDE4) and TNF production inhibitor with potential in the treatment of a variety of inflammatory and autoimmune diseases, particularly asthma, chronic obstructive pulmonary disease and chronic bronchitis. Other specifically claimed compounds from this series of amino(thio)phenols are:



Compound	A	Formula
294050	N	C ₁₆ H ₁₃ Cl ₂ F ₂ N ₃ O ₄
294052	N(O)	C ₁₆ H ₁₃ Cl ₂ F ₂ N ₃ O ₅

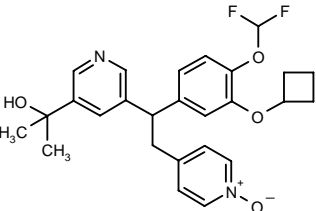
SOURCE – Darwin Discovery.

REFERENCES

1. Sharpe, A. and Kendall, H.J. (Darwin Discovery Ltd.) *Amino(thio)phenols and their therapeutic use*. WO 0048998.

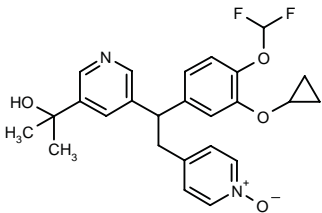
294224

2-[5-[1-[3-(Cyclobutyloxy)-4-(difluoromethoxy)phenyl]-2-(1-oxido-4-pyridinyl)ethyl]-3-pyridinyl]-2-propanol



C26 H28 F2 N2 O4; Mol wt: 470.5132

ACTION – Antiinflammatory agent, a phosphodiesterase type 4 (PDE4) inhibitor for the treatment of inflammatory airways disorders such as asthma. Another specifically claimed compound is:



294226: C25 H26 F2 N2 O4

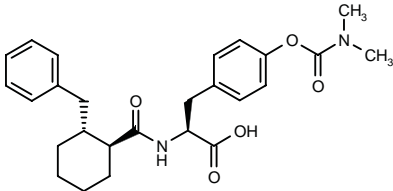
SOURCE – Merck Frosst.

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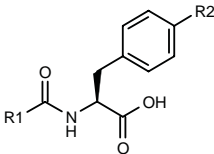
294553

N-[(1*S*,2*R*)-2-Benzylcyclohexylcarbonyl]-4-*O*-(dimethylcarbamoyl)-*L*-tyrosine



C26 H32 N2 O5; Mol wt: 452.5478

ACTION – $\alpha_4\beta_7$ integrin receptor antagonist that inhibits the adhesion of leukocytes, potentially useful in the treatment of inflammatory and immune disorders such as asthma, inflammatory bowel disease, transplant rejection, atherosclerosis, rheumatoid arthritis, etc. Other exemplified α -aminoacetic acid derivatives are:



Compound	R1	R2	Formula
294554	(1 <i>S</i> ,2 <i>R</i>)-2-(PhCH2)-cyclohexyl	4-thiomorpholinyl-CO2	C ₂₈ H ₃₄ N ₂ O ₅ S
294555	(1 <i>S</i> ,2 <i>R</i>)-2-(PhCH2)-cyclohexyl	1,1-dioxo-4-thiomorpholinyl-CO2	C ₂₈ H ₃₄ N ₂ O ₇ S
294556	(1 <i>S</i> ,2 <i>R</i>)-2-[3,5-(F)2-Ph-CH2]-cyclohexyl	OCON(Me)2	C ₂₆ H ₃₀ F ₂ N ₂ O ₅
294557	(1 <i>S</i> ,2 <i>R</i>)-2-[3,4-(F)2-PhCH2]-cyclohexyl	OCON(Me)2	C ₂₆ H ₃₀ F ₂ N ₂ O ₅
294558	(1 <i>S</i> ,2 <i>R</i>)-2-(3-Pyr-CH2)-cyclohexyl	OCON(Me)2	C ₂₅ H ₃₁ N ₃ O ₅
294559	(1 <i>S</i> ,2 <i>R</i>)-2-(4-Pyr-CH2)-cyclohexyl	OCON(Me)2	C ₂₅ H ₃₁ N ₃ O ₅
294560	4(S)-(PhCH2)-2-oxo-1,3-oxazolidin-5(R)-yl	OCON(Me)2	C ₂₃ H ₂₅ N ₃ O ₇
294561	4(S)-(PhCH2)-2-oxo-1,3-oxazolidin-5(R)-yl	H	C ₂₀ H ₂₀ N ₂ O ₅

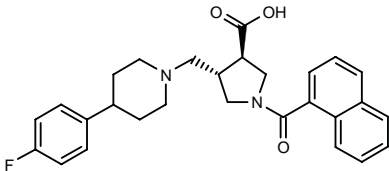
SOURCE – Elan.

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1. Konradi, A. et al. (Elan Pharmaceuticals, Inc.) *α -Aminoacetic acid derivs. useful as $\alpha_4\beta_7$ -receptor antagonists.* WO 0051974.

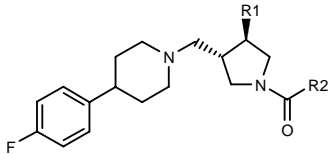
294596

(3*RS*,4*SR*)-4-[4-(4-Fluorophenyl)piperidin-1-ylmethyl]-1-(1-naphthylcarbonyl)pyrrolidine-3-carboxylic acid



C28 H29 F N2 O3; Mol wt: 460.5461

ACTION – Chemokine CCR3 and CCR5 receptor modulator, potentially useful for the treatment of inflammatory and immunoregulatory disorders such as asthma, allergic rhinitis, dermatitis and conjunctivitis, and autoimmune diseases such as rheumatoid arthritis and atherosclerosis. Based on the fact that HIV requires the CCR5 receptor for efficient entry into target cells, the compound is also expected to be useful for the treatment or prevention of HIV infection and AIDS. Other specifically claimed compounds within this series of pyrrolidines include the following:



Compound	R1	R2	Formula
294598	i-PrOCO	1-Naph	C ₃₁ H ₃₅ N ₂ O ₃
294599	Ac	1-Naph	C ₂₉ H ₃₁ N ₂ O ₂
294600	1,3-dithiolan-2-yl	1-Naph	C ₃₀ H ₃₃ FN ₂ OS ₂
294602	2-THF	1-Me-7-indolyl	C ₃₀ H ₃₆ FN ₃ O ₂
294603	4-(MeOCH2)-1,3-dioxolan-2-yl	2-Naph	C ₃₂ H ₃₇ N ₂ O ₄

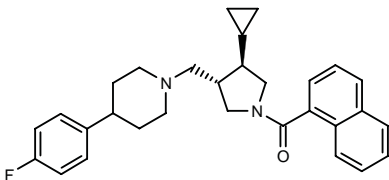
SOURCE – Merck & Co.

REFERENCES

1. Bao, J. et al. (Merck & Co., Inc.) *Pyrrolidine modulators of chemokine receptor activity.* WO 0051610.

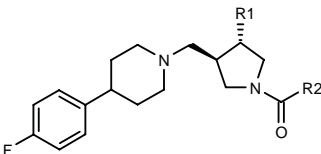
294597

1-[(3*RS*,4*SR*)-3-Cyclopropyl-4-[4-(4-fluorophenyl)piperidin-1-ylmethyl]pyrrolidin-1-yl]-1-(1-naphthyl)-methanone

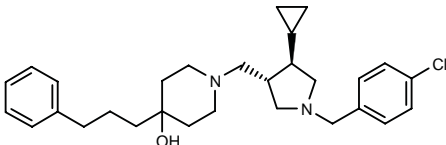


C30 H33 F N2 O; Mol wt: 456.6017

ACTION – Chemokine CCR3 and CCR5 receptor modulator, potentially useful for the treatment of inflammatory and immunoregulatory disorders such as asthma, allergic rhinitis, dermatitis and conjunctivitis, and autoimmune diseases such as rheumatoid arthritis and atherosclerosis. Based on the fact that HIV requires the CCR5 receptor for efficient entry into target cells, this compound is also expected to be useful for the treatment or prevention of HIV infection and AIDS. Other specifically claimed compounds within this series of 3-cyclopropyl- and 3-cyclobutyl-pyrrolidines include the following:



Compound	R1	R2	Formula
294604	cyclopropyl	2,4-(Cl)2-Ph	C ₂₆ H ₂₉ Cl ₂ FN ₂ O
294607	cyclopropyl	1-[MeO(CH ₂)3]-7-indolyl	C ₃₂ H ₄₀ FN ₃ O ₂
294609	cyclobutyl	1-Naph	C ₃₁ H ₃₅ FN ₂ O
294612	cyclobutyl	1-Me-7-indolyl	C ₃₀ H ₃₆ FN ₃ O



294601: C29 H39 Cl N2 O

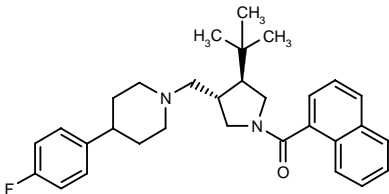
SOURCE – Merck & Co.

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1. Baker, R.K. et al. (Merck & Co., Inc.) *3-Cyclopropyl and 3-cyclobutyl pyrrolidine modulators of chemokine receptor activity*. WO 0051607.

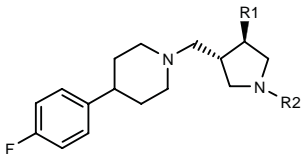
294605

1-[(3*RS*,4*RS*)-3-*tert*-Butyl-4-[4-(4-fluorophenyl)piperidin-1-ylmethyl]pyrrolidin-1-yl]-1-(1-naphthyl)methanone



C31 H37 F N₂ O; Mol wt: 472.6443

ACTION – Chemokine CCR3 and CCR5 receptor modulator, potentially useful for the treatment of inflammatory and immunoregulatory disorders such as asthma, allergic rhinitis, dermatitis and conjunctivitis, and autoimmune diseases such as rheumatoid arthritis and atherosclerosis. Based on the fact that HIV requires the CCR5 receptor for efficient entry into target cells, the compound is also expected to be useful for the treatment or prevention of HIV infection and AIDS. Other specifically claimed compounds within this series of 3-alkyl substituted pyrrolidines include the following:



Compound	R1	R2	Formula
294606	CF ₃	CH ₂ Ph	C ₂₄ H ₂₈ F ₄ N ₂
294608	CF ₃	1-(CO ₂ HCH ₂)-7-indolyl-CO	C ₂₈ H ₂₉ F ₄ N ₃ O ₃
294610	CH ₂ CH ₂ OH	1-Naph-CO	C ₂₉ H ₃₃ FN ₂ O ₂
294611	allyl-CH(OH)	1-Naph-CO	C ₃₁ H ₃₅ FN ₂ O ₂
294613	CH(OH)Ph	1-Me-7-indolyl-CO	C ₃₃ H ₃₆ FN ₃ O ₂
294614	CH ₂ OMe	1-Naph-CO	C ₂₉ H ₃₃ FN ₂ O ₂
294615	CH(Me)OAc	1-Naph-CO	C ₃₁ H ₃₅ FN ₂ O ₃

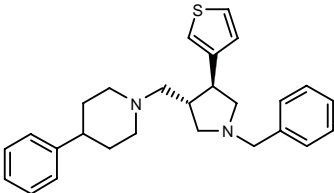
SOURCE – Merck & Co.

REFERENCES

1. Bao, J. et al. (Merck & Co., Inc.) *3-Alkyl substd. pyrrolidine modulators of chemokine receptor activity*. WO 0051609.

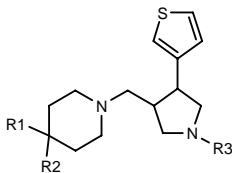
294616

1-[(3*RS*,4*RS*)-1-Benzyl-4-(3-thienyl)pyrrolidin-3-ylmethyl]-4-phenylpiperidine



C27 H32 N₂ S; Mol wt: 416.6298

ACTION – Chemokine CCR3 and CCR5 receptor modulator, potentially useful for the treatment of inflammatory and immunoregulatory disorders such as asthma, allergic rhinitis, dermatitis and conjunctivitis, and autoimmune diseases such as rheumatoid arthritis and atherosclerosis. Based on the fact that HIV requires the CCR5 receptor for efficient entry into target cells, this compound is also expected to be useful for the treatment or prevention of HIV infection and AIDS. Other specifically claimed compounds within this series of 3-thienyl- and 3-furanyl-pyrrolidines include the following:



Compound	R1	R2	R3	Isomer	Formula
294617	4-F-Ph	H	2,3-(OH)2-PhCO	3RS,4RS	C ₂₇ H ₂₅ FN ₂ O ₃ S
294618	4-F-Ph	H	3-indolyl-CO	3RS,4RS	C ₂₉ H ₃₀ FN ₃ OS
294619	(CH ₂) ₃ Ph	OH	3,4-(Me)2-PhCH ₂	3RS,4SR	C ₃₂ H ₄₂ N ₂ OS
294620	4-MeO- -Ph(CH ₂) ₃	OH	3,4-(Cl)2-PhCO	3RS,4SR	C ₃₁ H ₃₆ Cl ₂ N ₂ O ₃ S
294621	CH ₂ CH(OH)- -CH ₂ Ph	H	3,4-(Cl)2-PhCO	3RS,4SR	C ₃₀ H ₃₄ Cl ₂ N ₂ O ₂ S
294622	4-F-Ph	H	1-(HOCH ₂ CH ₂)- -7-benzimidazolyl-CO	3R,4R	C ₃₀ H ₃₃ FN ₄ O ₂ S
294623	4-F-Ph	H	7-benzoxazolyl-CO	3R,4R	C ₂₈ H ₂₈ FN ₃ O ₂ S
294624	3,4-(Cl)2- -PhCH ₂ OCH ₂	H	2,4-(Cl)2-PhCH ₂	3S,4S	C ₂₉ H ₃₂ Cl ₄ N ₂ OS

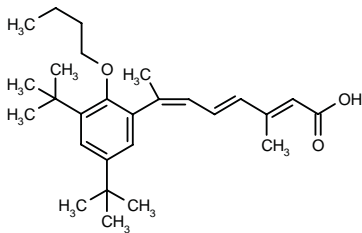
SOURCE – Merck & Co.

REFERENCES

1. Bao, J. et al. (Merck & Co., Inc.) 3-Thienyl and 3-furanyl pyrrolidine modulators of chemokine receptor activity. WO 0051608.

294727

7-(2-Butoxy-3,5-di-*tert*-butylphenyl)-3-methyl-2(*E*),4(*E*),6(*Z*)-octatrienoic acid



C27 H40 O3; Mol wt: 412.6100

ACTION – Retinoid X receptor (RXR) antagonist with potential for the treatment of T-helper cell type 2 (Th2)-mediated immune diseases such as IgE-mediated allergic diseases and diseases mediated by Th2-related cytokines such as IL-4 and IL-5, as well as for the treatment of osteoporosis and preneoplastic or neoplastic diseases, and for reducing or abolishing adverse events in patients receiving retinoid agonist treatment. Compound was shown to stimulate IL-12 production in activated human monocytes and THP-1 cells and to inhibit the differentiation of human naive T-cells into Th2 cells. When tested *in vivo* in mice, it was shown to dose-dependently inhibit inflammatory cell accumulation in a model of ovalbumin-induced airways inflammation following i.p. administration (10 and 30 mg/kg) and is reported to inhibit antigen-induced bronchoconstriction. In addition, it was shown to inhibit calcium release from neonatal murine calvaria induced by several different bone-resorbing agents. Tests in humans following topical application as a 1% cream twice daily revealed that it is effective in the treatment of multiple actinic keratoses and is well tolerated, in contrast to other retinoids.

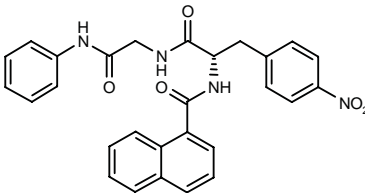
SOURCE – Roche.

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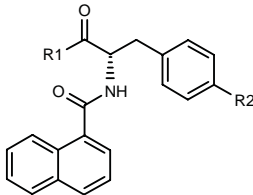
294743

N-[1(*S*)-(4-Nitrobenzyl)-2-oxo-2-[2-oxo-2-(phenylamino)ethylamino]ethyl]naphthalene-1-carboxamide



C28 H24 N4 O5; Mol wt: 496.5206

ACTION – Chemokine CCR3 receptor antagonist potentially useful for the treatment of allergic disorders such as bronchial asthma, eczema, allergic rhinitis, conjunctivitis, nasal polyposis, atopic dermatitis, pruritus and inflammatory bowel disease. Other exemplified compounds are:



Compound	R1	R2	Formula
294746	CH ₂ OPh	NO ₂	C ₂₇ H ₂₂ N ₂ O ₅
294748	CH ₂ SPh	NO ₂	C ₂₇ H ₂₂ N ₂ O ₄ S
294749	CH ₂ SO ₂ Ph	NO ₂	C ₂₇ H ₂₂ N ₂ O ₆ S
294751	CH ₂ NHPh	Cl	C ₂₇ H ₂₃ ClN ₂ O ₂
294752	-L-Ala-N(Me)Ph	NO ₂	C ₃₀ H ₂₈ N ₄ O ₅
294753	-L-Ala-NH(3-Pyr)	Cl	C ₂₈ H ₂₅ ClN ₄ O ₃
294754	-N(Me)-L-Ala-NHPh	Cl	C ₃₀ H ₂₈ ClN ₃ O ₃

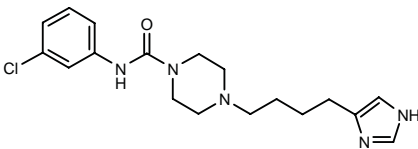
SOURCE – GlaxoSmithKline.

REFERENCES

1. Dhanak, D. and Knight, S.D. (SmithKline Beecham Corp.) CCR-3 receptor antagonists. WO 0053172.

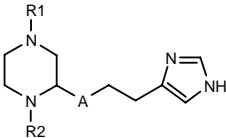
294755

N-(3-Chlorophenyl)-4-[4-(1*H*-imidazol-4-yl)butyl]-piperazine-1-carboxamide

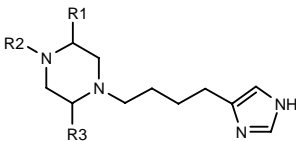


C18 H24 Cl N5 O; Mol wt: 361.8746

ACTION – Histamine H₃ receptor antagonist (K_i = 6 nM), potentially useful for the treatment of allergy, inflammation, hypertension, glaucoma, sleep disorders, gastrointestinal motility disorders, CNS hypo- or hyperactivity, Alzheimer's disease, schizophrenia and migraine. Also claimed is the use of this compound for the treatment of upper airways allergic responses in combination with histamine H₁ antagonists. Other exemplified imidazole compounds are:



Compound	R1	R2	A	Formula
294756	4-Cl-PhCH2	4-Cl-PhCH2	-(CH2)2-	C ₂₆ H ₃₀ Cl ₂ N ₄
294761	4-Cl-PhCH2	H	-CONHCH2CH2-	C ₁₉ H ₂₆ ClN ₅ O
294763	H	4-Cl-PhCH2	-CONHCH2CH2-	C ₁₉ H ₂₆ ClN ₅ O
294765	H	H	-CONH(CH2)3-	C ₁₃ H ₂₃ N ₅ O
294768	4-Cl-PhCH2	4-Cl-PhCH2	bond	C ₂₃ H ₂₆ Cl ₂ N ₄



Compound	R1	R2	R3	Formula
294757	H	4-Cl-PhCH2	CO2Et	C ₂₁ H ₂₉ ClN ₄ O ₂
294758	H	H	CO2Et	C ₁₄ H ₂₄ N ₄ O ₂
294760	CO2Et	4-Cl-PhCH2	H	C ₂₁ H ₂₉ ClN ₄ O ₂
294764	H	(E)-3-Pyr-CH=CHCO	H	C ₁₉ H ₂₅ N ₅ O
294770	H	(E)-COCH=CHPh	H	C ₂₀ H ₂₆ N ₄ O
294772	H	4-CF3-PhNHCO	H	C ₁₉ H ₂₄ F ₃ N ₅ O

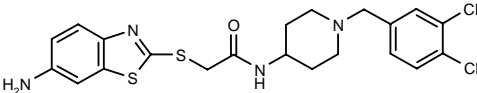
SOURCE – Schering-Plough.

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294813

2-(6-Aminobenzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)piperidin-4-yl]acetamide



C₂₁ H₂₂ Cl₂ N₄ O S₂; Mol wt: 481.4698

ACTION – Agent for the treatment of acute and chronic inflammatory disorders such as sepsis, pneumonia, arthritis and allergic diseases, as well as AIDS, cancer, ischemia/reperfusion disorders, arteriosclerosis and transplant rejection, a chemokine CCR3 receptor antagonist, as demonstrated in binding assays by inhibition of [¹²⁵I]-eotaxin binding to human CCR3 receptors expressed in CHO cells (IC₅₀ = 2.3 nM) and by inhibition of eotaxin-induced increases in Ca²⁺ concentrations in human eosinophils expressing the CCR3 receptor (IC₅₀ = 68 nM). A representative compound from a series of piperidine derivatives.

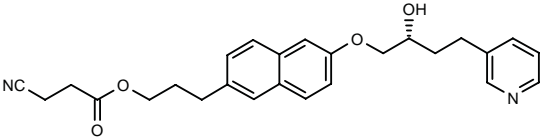
SOURCE – Banyu.

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1. Naya, A. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel piperidine derivs.* WO 0053600.

295242

3-Cyanopropionic acid 3-[6-[2(R)-hydroxy-4-(3-pyridinyl)butoxy]naphthalen-2-yl]propyl ester



C₂₆ H₂₈ N₂ O₄; Mol wt: 432.5172

ACTION – A representative compound from a series of mast cell inhibitors that are useful for the treatment of allergic diseases, especially rhinitis and asthma.

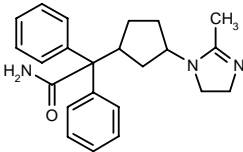
SOURCE – AstraZeneca.

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1. Tjörnebo, A. (AstraZeneca AB) *Novel cpds.* WO 0056714.

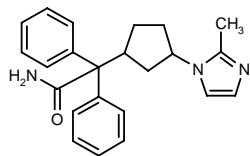
295267

2-[3-(2-Methyl-4,5-dihydro-1H-imidazol-1-yl)cyclopentyl]-2,2-diphenylacetamide



C₂₃ H₂₇ N₃ O; Mol wt: 361.4863

ACTION – Potent and selective muscarinic M₃ receptor antagonist, as demonstrated by pA₂ values of 8.8, 8.0 and 8.3, respectively, when tested *in vitro* for its ability to inhibit carbachol-induced contractions in M₃-bearing tissues, i.e., guinea pig trachea, bladder and ileum, while exhibiting lower affinity for M₂ receptors (pA₂ = 7.0 in guinea pig left atrial preparations). *In vivo*, it exhibited marked activity in inhibiting methacholine-induced bronchoconstriction in guinea pigs, with an ID₅₀ value of 3.2 µg/kg i.v., compared to an ID₅₀ value of 12.6 µg/kg i.v. for inhibition of oxotremorine-induced salivary secretion in rats; ID₅₀ values for atropine were 3.2 µg/kg i.v. and 6.3 µg/kg i.v., respectively. Potentially useful for the treatment of respiratory disorders such as chronic obstructive pulmonary disease, asthma, pulmonary fibrosis and rhinitis, gastrointestinal diseases such as irritable bowel syndrome and colitis, urinary disorders such as urinary incontinence and pollakiuria, and CNS disorders such as nausea, vomiting and motion sickness. Another exemplified compound from this series of imidazole derivatives is:



295268: C23 H25 N3 O

SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

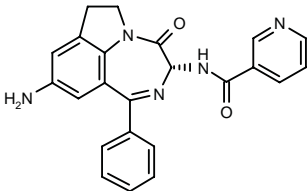
REFERENCES

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CI-1044

296398

N-[9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo-[3,2,1-*jk*][1,4]benzodiazepin-3(*R*)-yl]pyridine-3-carboxamide



C23 H19 N5 O2; Mol wt: 397.4361

ACTION – Potent and selective phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 0.27 μM in U973 cells; IC₅₀ > 100 μM against PDE3, PDE1 and PDE5). Compound inhibited lipopolysaccharide (LPS)-stimulated release of TNF-α from human peripheral blood monocytes and human whole blood (IC₅₀ = 0.34 and 1.24 μM, respectively), and it blocked antigen-induced eosinophil infiltration in rat bronchoalveolar lavage (ED₅₀ = 3.2 mg/kg p.o.) and inhibited LPS-induced TNF-α production in rats (ED₅₀ = 2.8 mg/kg p.o.). When compared to rolipram or Ariflo™, compound exhibited superior efficacy *in vivo* without producing emetic side effects. Potentially useful as an antiasthmatic and antiinflammatory agent.

SOURCE – Pfizer.

REFERENCES

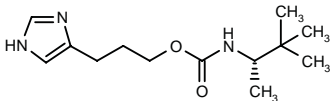
1. Pascal, Y. et al. (Institut de Recherche Jouveinal) *Diazepino-indoles as phosphodiesterase IV inhibitors.* EP 0828742, US 5972927, WO 9736905.

2. Burnouf, C. et al. *Synthesis, structure-activity relationships, and pharmacological profile of 9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-]indoles: Discovery of potent, selective phosphodiesterase type 4 inhibitors.* J Med Chem 2000, 43(25): 4850.

FUB-593⁴

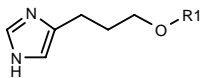
296472

N-[1(*S*),2,2-Trimethylpropyl]carbamic acid 3-(1*H*-imidazol-4-yl)propyl ester



C13 H23 N3 O2; Mol wt: 253.3437

ACTION – Histamine H₃ receptor agonist proven to decrease *tele*-methylhistamine levels in mouse cerebral cortex after oral administration with an ED₅₀ of 0.27 mg/kg. Potentially useful for the treatment of neurogenic airways inflammation, migraine or sleep disorders and as a pharmacological tool. Other related compounds are:



Compound	R1	Formula
FUB-407 [281395]^{*,1,3,4}	t-BuCH2CH2	C ₁₂ H ₂₂ N ₂ O
FUB-557 [290434]^{2,4}	CONHCH(2-thienyl)-Ph	C ₁₈ H ₁₉ N ₃ O ₂ S

SOURCES – Bioprojet; INSERM, Paris Cedex (FR).

REFERENCES

1. Schwartz, J.-C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale];Societe Civile Bioprojet) *Imidazole derivs. as histamine receptor H3 (ant)agonists.* EP 0760811, FR 2732017, JP 1998501001, WO 9629315.

2. Sasse, A. et al. *(Partial) agonist/antagonist properties of novel diarylalkyl carbamates on histamine H3 receptors.* Bioorg Med Chem 2000, 8(5): 1139.

3. Sasse, A. et al. *Novel partial agonists for the histamine H3 receptor with high in vitro and in vivo activity.* J Med Chem 1999, 42(20): 4269.

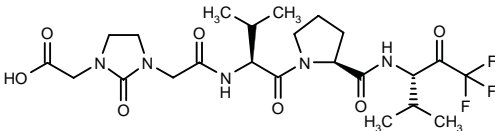
4. Schunack, W. et al. *Partial agonists for the histamine H3 receptor with high in vivo activity.* Int Sendai Histamine Symp (Nov 22-25, Sendai) 2000, Abst 0-10.

*Identified compound **281395** Drug Data Report 2000, 022(01): 0104.

**AGENTS FOR RESPIRATORY
DISTRESS SYNDROME**

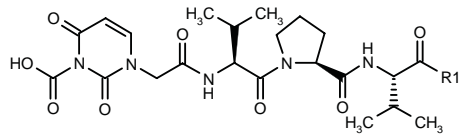
294800

1-[*N*-[2-[3-(Carboxymethyl)-2-oxoimidazolidin-1-yl]acetyl]-L-valyl-L-prolyl-L-valyl]trifluoromethane



C23 H34 F3 N5 O7; Mol wt: 549.5436

ACTION – Human neutrophil elastase inhibitor (IC_{50} = 0.010 μ M) proven to decrease neutrophil elastase-induced pulmonary hemorrhage in hamsters by 61 and 97%, respectively, when administered as a single i.v. bolus of 3 and 10 mg/kg, and by 54, 71 and 94%, respectively, at doses of 1, 3 and 10 mg/kg/h i.v. for 70 min. No acute toxicity was observed in mice following a single i.v. dose of 300 mg/kg. This compound displayed high water solubility (> 1000 mg/ml) at room temperature and pH 7.4 and 2.3. Particularly useful for the treatment of acute pulmonary disease. Other exemplified heterocyclic compounds are:



Compound	R1	Formula
294801	2-benzoxazolyl	C ₂₉ H ₃₄ N ₆ O ₉
294802	CONHCH ₂ Ph	C ₃₀ H ₃₈ N ₆ O ₉

SOURCE – Dainippon Pharmaceutical.

REFERENCES

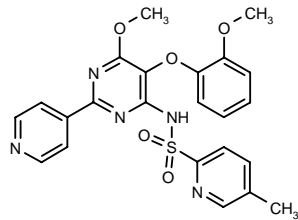
1. Sato, F. et al. (Dainippon Pharmaceutical Co., Ltd.) *Heterocyclic cpds., intermediates thereof and elastase inhibitors*. JP 2000256396, WO 0052032.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

294458

N-[6-Methoxy-5-(2-methoxyphenoxy)-2-(4-pyridyl)pyrimidin-4-yl]-5-methylpyridine-2-sulfonamide



C23 H21 N5 O5 S; Mol wt: 479.5149

ACTION – Endothelin receptor antagonist shown to inhibit endothelin binding to recombinant human ET_A receptors expressed in baculovirus-infected insect cells (IC_{50} = 50 nM or less) and to inhibit endothelin-induced contractions in isolated rat aorta rings (pA_2 = 8.0 or higher). Peak plasma concentrations of 1500 ng/ml or higher and an AUC of 10,000 ng.h/ml or greater were determined when the compound was administered to rats at 5 mg/kg by gavage. The compound is indicated for the treatment of disorders associated with abnormal vascular tone and endothelial dysfunction including heart failure, hypertension, acute ischemic coronary syndrome, angina pectoris, renal failure, etc.

SOURCE – Roche.

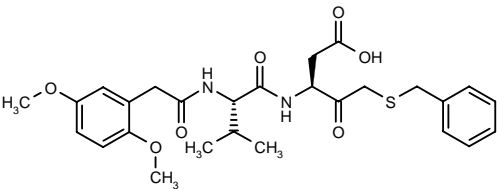
REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *4-Heterocyclisulfonamidyl-6-methoxy-5-(2-methoxy-phenoxy)-2-pyridyl-pyrimidine derivs., their preparation and use as endothelin receptor antagonists*. WO 0052007.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

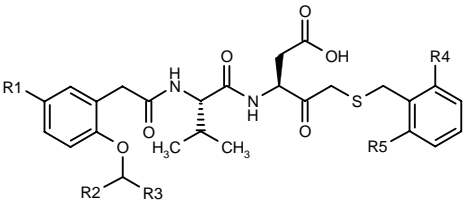
294951

5-(Benzylsulfanyl)-3(*S*)-[*N*-[2-(2,5-dimethoxyphenyl)-acetyl]-L-valylamino]-4-oxopentanoic acid



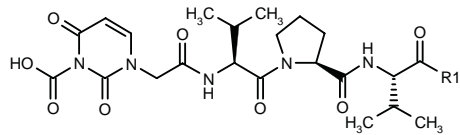
C27 H34 N2 O7 S; Mol wt: 530.6386

ACTION – Caspase 3 inhibitor potentially useful for the treatment of cardiac and cerebral ischemia/reperfusion injury, type 1 diabetes, AIDS, cerebral and spinal cord trauma, organ damage during transplantation, alopecia, aging, Parkinson's disease, Alzheimer's disease, Down's syndrome, spinal muscular atrophy, multiple sclerosis and neurodegenerative disorders. The compound was able to reduce infarct size in rats subjected to 45 min of regional ischemia and 3 h of reperfusion when given as a first bolus 5 min before the onset of ischemia and a second bolus at the onset of reperfusion. Other exemplified γ -ketoacid dipeptides are:



Compound	R1	R2	R3	R4	R5	Formula
294952	SO ₂ Me	H	H	Cl	F	C ₂₇ H ₃₂ ClFN ₂ O ₈ S ₂
294953	OCH ₂ CO ₂ Me	H	Me	H	H	C ₃₀ H ₃₈ N ₂ O ₉ S
294954	i-PrOCOCH ₂ O	H	Me	Cl	F	C ₃₂ H ₄₀ ClFN ₂ O ₉ S
294955	OCH ₂ CO ₂ H	H	Me	Cl	F	C ₂₉ H ₃₄ ClFN ₂ O ₉ S
294956	2-pyrimidinyl-O	H	Me	Cl	F	C ₃₁ H ₃₄ ClFN ₄ O ₇ S
294957	CH=CHCO ₂ H	H	H	Cl	F	C ₂₈ H ₃₂ ClFN ₂ O ₈ S
294958	CH ₂ CH ₂ CO ₂ H	H	H	Cl	F	C ₂₉ H ₃₄ ClFN ₂ O ₈ S
294959	CH=CHCO ₂ H	H	Me	Cl	F	C ₃₀ H ₃₄ ClFN ₂ O ₉ S
294960	OMe	F	F	Cl	F	C ₂₇ H ₃₀ ClF ₃ N ₂ O ₇ S
294961	SO ₂ Me	F	F	Cl	F	C ₂₇ H ₃₀ ClF ₃ N ₂ O ₈ S ₂
294962	SO ₂ Ph	H	Me	Cl	F	C ₃₃ H ₃₆ ClFN ₂ O ₈ S ₂
294963	3-Me-1,2,4-oxadiazol-5-yl	H	H	Cl	F	C ₂₉ H ₃₂ ClFN ₄ O ₇ S

ACTION – Human neutrophil elastase inhibitor (IC_{50} = 0.010 μ M) proven to decrease neutrophil elastase-induced pulmonary hemorrhage in hamsters by 61 and 97%, respectively, when administered as a single i.v. bolus of 3 and 10 mg/kg, and by 54, 71 and 94%, respectively, at doses of 1, 3 and 10 mg/kg/h i.v. for 70 min. No acute toxicity was observed in mice following a single i.v. dose of 300 mg/kg. This compound displayed high water solubility (> 1000 mg/ml) at room temperature and pH 7.4 and 2.3. Particularly useful for the treatment of acute pulmonary disease. Other exemplified heterocyclic compounds are:



Compound	R1	Formula
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294802	CONHCH ₂ Ph	C ₃₀ H ₃₈ N ₆ O ₉

SOURCE – Dainippon Pharmaceutical.

REFERENCES

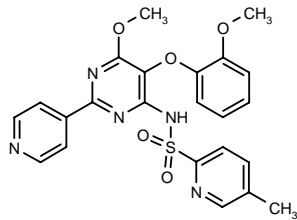
1. Sato, F. et al. (Dainippon Pharmaceutical Co., Ltd.) *Heterocyclic cpds., intermediates thereof and elastase inhibitors*. JP 2000256396, WO 0052032.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

294458

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C23 H21 N5 O5 S; Mol wt: 479.5149

ACTION – Endothelin receptor antagonist shown to inhibit endothelin binding to recombinant human ET_A receptors expressed in baculovirus-infected insect cells (IC_{50} = 50 nM or less) and to inhibit endothelin-induced contractions in isolated rat aorta rings (pA_2 = 8.0 or higher). Peak plasma concentrations of 1500 ng/ml or higher and an AUC of 10,000 ng.h/ml or greater were determined when the compound was administered to rats at 5 mg/kg by gavage. The compound is indicated for the treatment of disorders associated with abnormal vascular tone and endothelial dysfunction including heart failure, hypertension, acute ischemic coronary syndrome, angina pectoris, renal failure, etc.

SOURCE – Roche.

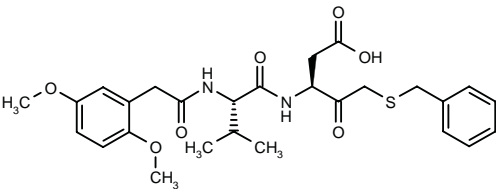
REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *4-Heterocyclisulfonamidyl-6-methoxy-5-(2-methoxy-phenoxy)-2-pyridyl-pyrimidine derivs., their preparation and use as endothelin receptor antagonists*. WO 0052007.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

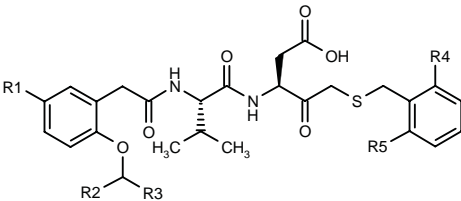
294951

5-(Benzylsulfanyl)-3(*S*)-[*N*-[2-(2,5-dimethoxyphenyl)-acetyl]-L-valylamino]-4-oxopentanoic acid



C27 H34 N2 O7 S; Mol wt: 530.6386

ACTION – Caspase 3 inhibitor potentially useful for the treatment of cardiac and cerebral ischemia/reperfusion injury, type 1 diabetes, AIDS, cerebral and spinal cord trauma, organ damage during transplantation, alopecia, aging, Parkinson's disease, Alzheimer's disease, Down's syndrome, spinal muscular atrophy, multiple sclerosis and neurodegenerative disorders. The compound was able to reduce infarct size in rats subjected to 45 min of regional ischemia and 3 h of reperfusion when given as a first bolus 5 min before the onset of ischemia and a second bolus at the onset of reperfusion. Other exemplified γ -ketoacid dipeptides are:



Compound	R1	R2	R3	R4	R5	Formula
294952	SO ₂ Me	H	H	Cl	F	C ₂₇ H ₃₂ ClF ₂ N ₂ O ₈ S ₂
294953	OCH ₂ CO ₂ Me	H	Me	H	H	C ₃₀ H ₃₈ N ₂ O ₉ S
294954	i-PrOCOCH ₂ O	H	Me	Cl	F	C ₃₂ H ₄₀ ClF ₂ N ₂ O ₉ S
294955	OCH ₂ CO ₂ H	H	Me	Cl	F	C ₂₉ H ₃₄ ClF ₂ N ₂ O ₉ S
294956	2-pyrimidinyl-O	H	Me	Cl	F	C ₃₁ H ₃₄ ClF ₂ N ₄ O ₇ S
294957	CH=CHCO ₂ H	H	H	Cl	F	C ₂₈ H ₃₂ ClF ₂ N ₂ O ₈ S
294958	CH ₂ CH ₂ CO ₂ H	H	H	Cl	F	C ₂₉ H ₃₄ ClF ₂ N ₂ O ₈ S
294959	CH=CHCO ₂ H	H	Me	Cl	F	C ₃₀ H ₃₄ ClF ₂ N ₂ O ₉ S
294960	OMe	F	F	Cl	F	C ₂₇ H ₃₀ ClF ₃ N ₂ O ₇ S
294961	SO ₂ Me	F	F	Cl	F	C ₂₇ H ₃₀ ClF ₃ N ₂ O ₈ S ₂
294962	SO ₂ Ph	H	Me	Cl	F	C ₃₃ H ₃₆ ClF ₂ N ₂ O ₈ S ₂
294963	3-Me-1,2,4-oxadiazol-5-yl	H	H	Cl	F	C ₂₉ H ₃₂ ClF ₂ N ₄ O ₇ S

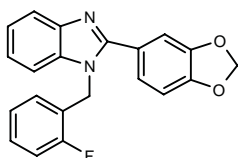
SOURCE – Merck Frosst.

REFERENCES

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295140

2-(1,3-Benzodioxol-5-yl)-1-(2-fluorobenzyl)-1H-benzimidazole



C21 H15 F N2 O2; Mol wt: 346.3595

ACTION – Selective inhibitor of cGMP phosphodiesterase (cGMP-PDE), as demonstrated by an IC_{50} value of 0.004 μ M against cGMP-PDE compared to values > 100 μ M against both cAMP-PDE and calcium/calmodulin-dependent cGMP-PDE. Potentially useful in the treatment of cardiovascular disorders such as stable, unstable and variant angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis and thrombosis, as well as glaucoma, sexual dysfunction and asthma. A specifically claimed compound from a series of bicyclic imidazolyl derivatives.

SOURCE – Pharmacia.

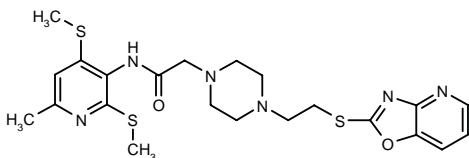
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K-10085*

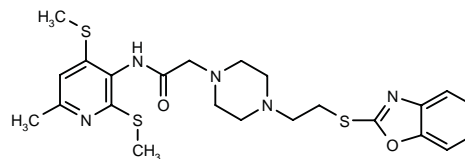
272105

N-[6-Methyl-2,4-bis(methylsulfanyl)-3-pyridinyl]-2-[4-[2-(oxazolo[4,5-*b*]pyridin-2-ylsulfanyl)ethyl]-1-piperazinyl]acetamide



C22 H28 N6 O2 S3; Mol wt: 504.7012

ACTION – ACAT inhibitor with some degree of selectivity for aortic enzyme (IC_{50} = 0.12 and 0.21 μ M for inhibition of ACAT activity in rabbit aortic and intestinal microsomes, respectively) and an IC_{50} value of 0.10 μ M for inhibition of ACAT activity in J774A.1 cells. Compound showed good bioavailability and significantly and dose-dependently reduced fatty streak area in the aortic arch in Golden Syrian hamsters at doses (3-10 mg/kg p.o.) which did not affect plasma cholesterol. Another related compound is:



K-10081 [296943]: C23 H29 N5 O2 S3

SOURCE – Kowa.

REFERENCES

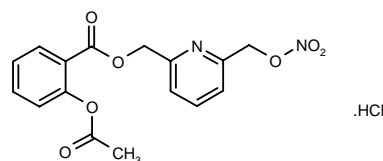
1. Shibuya, K. et al. (Kowa Co., Ltd.) *Novel cyclic diamine cpds. and medicine containing the same*. EP 0987254, WO 9854153.
2. Shibuya, K. et al. *Design and synthesis of aortic-selective ACAT inhibitor*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 2P-04.

*Identified compound **272105** (see **272096**) Drug Data Rep 1999, 021(03): 0279.

NCX-4050

294428

2-Acetoxybenzoic acid 6-(nitrooxymethyl)pyridin-2-yl-methyl ester hydrochloride



C16 H14 N2 O7 . HCl; Mol wt: 382.7545

ACTION – Cyclooxygenase inhibitor, a nitrooxy derivative of acetylsalicylic acid with antiinflammatory, analgesic and antithrombotic properties. This compound can be solubilized without using surfactants or apolar solvents and can be formulated without excipients that produce irritant effects, resulting in improved activity, low toxicity and better systemic absorption than prior art nitroxy compounds. NCX-4050 inhibited rabbit aorta and corpus cavernosum smooth muscle contractions by 87% and 85%, respectively, at 0.1 mM and by 80% and 63%, respectively, at 0.01 mM. It also potently inhibited human vascular smooth muscle cell proliferation.

SOURCE – NicOx.

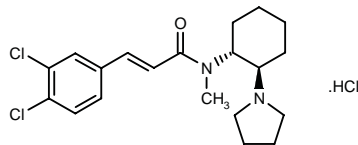
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ANTIARRHYTHMIC DRUGS

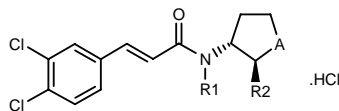
294483

3-(3,4-Dichlorophenyl)-N-methyl-N-[(1*RS*,2*RS*)-2-(1-pyrrolidinyl)cyclohexyl]-2(*E*)-propenamide hydrochloride



C20 H26 Cl2 N2 O . HCl; Mol wt: 417.8053

ACTION – Antiarrhythmic and local analgesic and anesthetic agent, a cardiac sodium and potassium channel blocker, as demonstrated by its ability to increase P-R and Q-T intervals in rats (ED₂₅ = 2.8 and 8 μmol/kg i.v., respectively). Compound exhibited potent antiarrhythmic activity in rats subjected to coronary artery occlusion (ED₅₀ = 0.4 μmol/kg/min), and was found to be effective in canine models of vagal atrial fibrillation and sterile pericarditis. Also reported to be useful for the treatment of a broad range of disorders including convulsions, epilepsy, depression, anxiety, asthma, arthritis, allergy, gastrointestinal disorders, ischemia, hypertension and diabetes. Other specifically claimed compounds from this series of aminocycloalkyl cinnamide derivatives are:



Compound	R1	R2	A	Formula
294484	H	4-morpholynyl	-(CH2)2-	C ₁₉ H ₂₄ Cl ₂ N ₂ O ₂ .HCl
294485	Me	1-pyrrolidinyl	-CH2-	C ₁₉ H ₂₄ Cl ₂ N ₂ O.HCl

SOURCE – Nortran.

REFERENCES

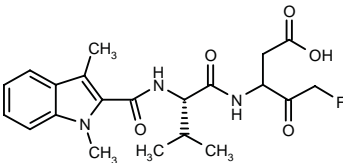
1. Beatch, G.N. et al. (Nortran Pharmaceuticals Inc.) *Aminocycloalkyl cinnamide cpds. for arrhythmia and as analgesics and anesthetics*. WO 0051981.

HEART FAILURE THERAPY

IDN-1965

274789

3-[2(*S*)-(1,3-Dimethyl-1*H*-indol-2-ylcarboxamido)-3-methylbutanamido]-5-fluoro-4-oxopentanoic acid



C21 H26 F N3 O5; Mol wt: 419.4504

ACTION – Irreversible caspase inhibitor with preferential activity against caspases 6, 8 and 9 (K_i = 41, 62 and 25 nM, respectively) over caspases 1, 2 and 3 (K_i > 500 nM), proven to protect Jurkat cells from apoptosis induced by anti-Fas. *In vivo* in a model of cold ischemia/warm reperu-sion liver injury in rats, compound was seen to reduce endothelial cell apoptosis and to prolong survival after orthotopic liver transplant. In a model of apoptosis-induced heart disease in transgenic mice expressing a ligand-activatable procaspase 8, compound markedly delayed death from 4.1 h in vehicle-treated animals to 57.1 h, almost completely prevented left ventricular dilatation and improved fractional shortening. In addition, in a peripartum cardiomyopathy model in Gαq transgenic mice, compound decreased the frequency of cardiac myocyte apoptosis and preserved cardiac mass. Potentially useful for the treatment of dilated cardiomyopathy.

SOURCE – Idun Pharmaceuticals.

REFERENCES

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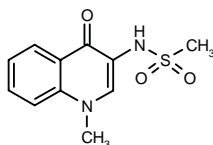
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LAS-31180

296444

N-(1-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)methanesulfonamide



C11 H12 N2 O3 S; Mol wt: 252.2928

ACTION – Positive inotropic and vasodilating agent, a selective inhibitor of phosphodiesterase type 3 (PDE3; $IC_{50} = 9.7 \mu M$; $IC_{50} > 1000 \mu M$ against PDE1, PDE2, PDE4 and PDE5). Compound exhibited a positive inotropic effect in isolated guinea pig ventricular strips and a mild inotropic effect in isolated guinea pig working hearts. In conscious dogs, it induced a dose-dependent and long-lasting positive inotropic effect after i.v. and oral administration, with minimal effect on heart rate. In conscious renal hypertensive dogs, compound given by i.v. bolus was found to induce significant and dose-related decreases in mean blood pressure, with a 20% fall at 3.8 mg/kg, accompanied by tachycardia at higher doses (30 mg/kg); orally administered compound induced a long-lasting hypotensive effect at 1 mg/kg, with minimal tachycardia. Potentially useful for the treatment of congestive heart failure.

SOURCE – Almirall Prodesfarma.

REFERENCES

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LEVOSIMENDAN⁺

Rec INN; USAN

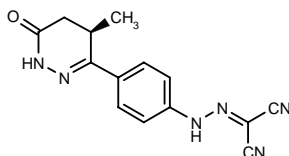
189761

(*R*)-(-)-2-[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenylhydrazono]propanedinitrile

(*R*)-(-)-2-[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenylhydrazono]malonodinitrile

(*R*)-(-)-6-[4-(1,1-Dicyanomethylenehydrazino)phenyl]-5-methyl-2,3,4,5-tetrahydropyridazin-3-one

(-)-OR-1259



C14 H12 N6 O; Mol wt: 280.2898

ACTION – Calcium sensitizer and vasodilator that acts as a vascular smooth muscle and cardiac cell potassium channel opener.

INDICATION — Treatment of acute heart failure or refractory symptoms of chronic heart failure.

PRESENTATION – Solution for i.v. infusion, 2.5 mg/ml.

PROPRIETARY NAME – *Simdax* (SE).

SOURCES – Abbott; Orion.

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3. Janssen, P.M.L. et al. *Levosimendan improves diastolic and systolic function in failing human myocardium.* *Eur J Pharmacol* 2000, 404(1-2): 191.
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5. Levijoki, J. et al. *The vasodilatory effects of levosimendan are not mediated through phosphodiesterase inhibition.* *Eur Heart J* 2000, 21(Suppl.): Abst P2181.
6. Lochner, A. et al. *Effect of a calcium-sensitizing agent, levosimendan, on the postcardioplegic inotropic response of the myocardium.* *Cardiovasc Drugs Ther* 2000, 14(3): 271.
7. Nieminen, M.S. et al. *Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure.* *J Am Coll Cardiol* 2000, 36(6): 1903.
8. Slawsky, M.T. et al. *Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure.* *Circulation* 2000, 102(18): 2222.
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12. Takahashi, R. et al. *Effects of OR-1896, an active metabolite of levosimendan, on contractile force and aequorin light transients in intact rabbit ventricular myocardium.* *J Cardiovasc Pharmacol* 2000, 36(1): 118.
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14. Toivonen, L. et al. *Electrophysiologic effects of a calcium sensitizer inotropic levosimendan administered intravenously in patients with normal cardiac function.* *J Cardiovasc Pharmacol* 2000, 35(4): 664.
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17. *Orion updates product pipeline.* *DailyDrugNews.com* (Daily Essentials) 2000, May 11.
18. *Simdax approved in Sweden for severe heart failure.* *DailyDrugNews.com* (Daily Essentials) 2000, Sept 28.

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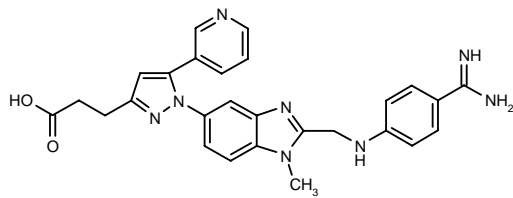
⁺Drug Data Rep 1993, 015(02): 0149.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

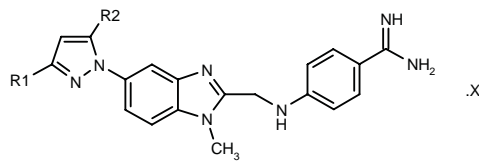
294205

3-[1-[2-(4-Amidinophenylaminomethyl)-1-methyl-1H-benzimidazol-5-yl]-5-(3-pyridyl)-1H-pyrazol-3-yl]propionic acid



C27 H26 N8 O2; Mol wt: 494.5564

ACTION – Anticoagulant, a thrombin inhibitor useful for the treatment of venous and arterial thrombotic diseases. The compound prolonged thrombin time (TT) with an ED₂₀₀ (concentration doubling TT) of 0.510 µM. Other exemplified substituted bicyclic heterocycles include the following:



Compound	R1	R2	X	Formula
294206	Me	Ph	HCl	C ₂₆ H ₂₅ N ₇ ·HCl
294207	CH ₂ CH ₂ CO ₂ Et	Ph	HCl	C ₃₀ H ₃₁ N ₇ O ₂ ·HCl
294208	CO ₂ H	2-thienyl		C ₂₄ H ₂₁ N ₇ O ₂ S

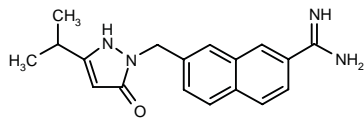
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Haeuel, N. et al. (Boehringer Ingelheim Pharma KG) *Substd. bicyclic heterocycles and the use thereof as thrombin inhibitors*. DE 19907813, WO 0050419.

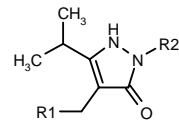
294566

7-(3-Isopropyl-5-oxo-2,5-dihydro-1H-pyrazol-1-ylmethyl)naphthalene-2-carboxamidine



C18 H20 N4 O; Mol wt: 308.3830

ACTION – Anticoagulant, a factor Xa inhibitor potentially useful for the treatment of thrombosis, myocardial infarction, atherosclerosis, inflammation, stroke, angina pectoris, restenosis following angioplasty and intermittent claudication. Other specifically claimed pyrazol-3-one derivatives are:



Compound	R1	R2	Formula
294567	7-[NH ₂ C(=NH)]-2-Naph	7-[NH ₂ C(=NH)]-2-Naph-CH ₂	C ₃₀ H ₃₀ N ₆ O
294568	3-[NH ₂ C(=NH)]-Ph	3-[NH ₂ C(=NH)]-PhCH ₂	C ₂₂ H ₂₆ N ₆ O
294569	7-[NH ₂ C(=NH)]-2-Naph	3-[NH ₂ C(=NH)]-PhCH ₂	C ₂₆ H ₂₈ N ₆ O
294570	7-[NH ₂ C(=NH)]-2-Naph	H	C ₁₈ H ₂₀ N ₄ O

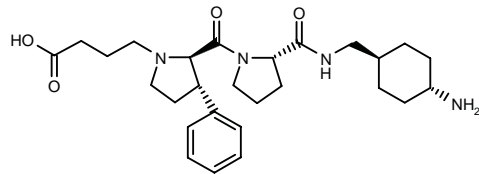
SOURCE – Merck KGaA.

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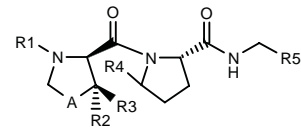
294820

N-(3-Carboxypropyl)-[3(S)-phenyl]-D-prolyl-L-proline *trans*-4-aminocyclohexylmethylamide



C27 H40 N4 O4; Mol wt: 484.6370

ACTION – Anticoagulant and antithrombotic agent, a thrombin inhibitor reported to exhibit oral bioavailability and minimal side effects. Other exemplified compounds from this series of substituted proline derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
294822	H	Et	H	H	trans-4-NH ₂ -cyclohexyl	C ₁₉ H ₃₄ N ₄ O ₂
294823	CH ₂ CH ₂ OMe	Et	H	H	trans-4-NH ₂ -cyclohexyl	C ₂₂ H ₄₀ N ₄ O ₃
294824	(CH ₂) ₃ CO ₂ H	Ph	H	H	6-NH ₂ -3-Pyr	C ₂₆ H ₃₃ N ₅ O ₄
294825	t-BuOCO	Me	Me	H	6-NH ₂ -3-Pyr	C ₂₂ H ₃₃ N ₅ O ₄ S
294827	H	H	H	Pr	4-NH ₂ -cyclohexyl	C ₂₀ H ₃₆ N ₄ O ₂
294828	SO ₂ CH ₂ Ph	OEt	H	H	6-NH ₂ -2-Me-3-Pyr	C ₂₆ H ₃₈ N ₅ O ₃ S

SOURCE – C & C Research.

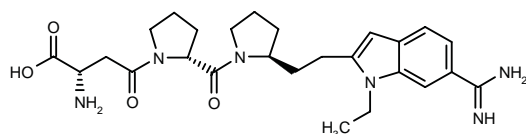
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AT-1362

296941

4-[2(*R*)-[2(*S*)-[2-(6-Amidino-1-ethylindol-2-yl)ethyl]-pyrrolidin-1-ylcarbonyl]pyrrolidin-1-yl]-2(*S*)-amino-4-oxobutyric acid



C26 H36 N6 O4; Mol wt: 496.6084

ACTION – Anticoagulant, a potent, competitive and orally active inhibitor of thrombin ($K_i = 6.7$ nM) with > 16-fold selectivity over other serine proteases including trypsin, factor Xa, factor XIa, activated protein C, kallikrein, plasmin, urokinase and tPA. In a rat model of venous thrombosis induced by partial stasis and endothelial disruption, compound was more potent than argatroban, with ID_{50} values of 0.03 mg/kg i.v. plus 0.5 µg/kg/min and 0.13 mg/kg i.v. plus 8.7 µg/kg/min, respectively, for inhibiting thrombus formation. A significant decrease in thrombus formation at 1-4 h after dosing was also seen in this model when compound were given orally at 30 and 100 mg/kg. It was more effective than argatroban in prolonging bleeding time in rats, giving a 2-fold prolongation of bleeding at a dose of 0.56 mg/kg i.v., compared to 1.1 mg/kg i.v. for the reference compound. In the $FeCl_2$ -induced rat carotid artery thrombosis model, compound promoted vessel patency, with a significant effect at a dose of 0.3 mg/kg i.v. plus 5 µg/kg/min.

SOURCES – C & C Research; Chugai.

REFERENCES

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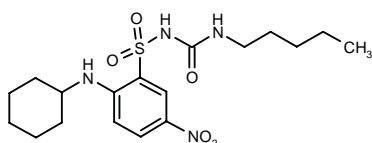
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ANTIPLATELET THERAPY

BM-567

296796

2-(Cyclohexylamino)-5-nitro-*N*-(pentylcarbamoyl)-benzenesulfonamide



C18 H28 N4 O5 S; Mol wt: 412.5082

ACTION – Antiplatelet agent, a torasemide derivative that acts as a thromboxane A_2 (TxA_2) receptor antagonist and thromboxane synthase inhibitor. Compound exhibited greater affinity for TxA_2 receptors than sulotroban and SQ-29548 ($IC_{50} = 1.1$, 930 and 21 nM, respectively) and inhibited arachidonic acid- ($ED_{100} = 0.50$ µM), U-46619- ($ED_{50} = 0.298$ µM) and collagen-induced (44.3% at 10 µM) aggregation of human platelet-rich plasma, as well as the second wave of ADP-induced aggregation. In addition, compound induced a significant prolongation of the closure time (CT, measured by the platelet function analyzer PFA-100®) in human whole blood and completely prevented (at 1 µM) TxB_2 production in arachidonic acid-activated platelets.

SOURCES – University of Liège, Liège (BE); University of Namur, Namur (BE).

REFERENCES

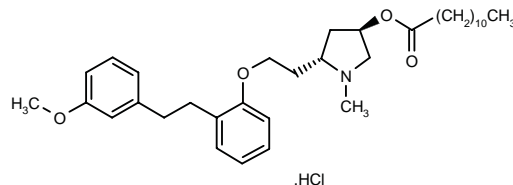
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R-102444^{1,3}

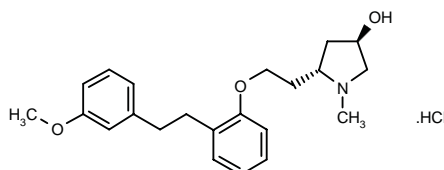
296245

Dodecanoic acid 5(*R*)-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]pyrrolidin-3(*R*)-yl ester hydrochloride



C34 H51 N O4 . HCl; Mol wt: 574.2408

ACTION – Antithrombotic agent, the lauryl ester prodrug of the potent and selective 5-HT₂ receptor ligand **R-96544**. The prodrug shows weak activity *in vitro* ($IC_{50} = 240$ nM for binding affinity at 5-HT₂ receptors) but inhibited 5-HT-induced rat platelet aggregation *ex vivo* by 74.9% at 1 mg/kg p.o., with comparable potency to the active compound but without gastric toxicity; for comparison, sarpogrelate produced only 21.3% inhibition of 5-HT-induced platelet aggregation at a dose of 10 mg/kg p.o. In the rat photochemically induced thrombosis model, it prolonged the time required for thrombotic occlusion of the artery in a dose-dependent manner, with a significant effect at 3 mg/kg p.o.; in this model, sarpogrelate at a dose of 30 mg/kg p.o. produced only a modest, nonsignificant effect.



R-96544 [212779]^{*,2-4}: C22 H29 N O3.HCl

SOURCE – Sankyo.

REFERENCES

1. Asai, F. and Fujimoto, K. (Sankyo Co., Ltd.) *Compsn. containing diarylalkane deriv. as the active ingredient for treating or preventing pancreatitis*. JP 1998212232, WO 9823271.

2. Fujimoto, K. et al. (Sankyo Co., Ltd.). *Phenoxyalkylamines, -pyrrolidines and -piperidines for the treatment and prevention of circulatory diseases and psychosis*. EP 0600717, JP 1994234736, JP 1994306025, US 5556864.

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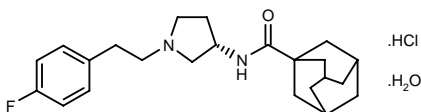
4. Tanaka, N. et al. *Antiplatelets with 5-HT₂ receptor antagonistic action - Synthesis and structure activity relationships of [2-(ω-phenylalkyl)phenoxyalkylamines*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-01.

*Identified compound **212779** (see **211599**) Drug Data Rep 1994, 016(10): 0885.

Y-39241*

289794

N-[1-[2-(4-Fluorophenyl)ethyl]pyrrolidin-3(*S*)-yl]adamantane-1-carboxamide hydrochloride hydrate



C₂₃ H₃₁ F N₂ O . HCl . H₂O; Mol wt: 424.9846

ACTION – Antiplatelet agent, a potent and selective 5-HT₂ receptor antagonist ($K_i = 0.09$ and 79 nM, respectively, for binding affinity at rat 5-HT₂ and 5-HT_{1A} receptors) proven to prevent collagen-induced rabbit platelet aggregation *in vitro* ($IC_{50} = 1.9$ nM). In a model of thromboembolic death induced by collagen plus 5-HT in mice, compound reduced the mortality rate in a dose-dependent manner with efficacy superior to the reference 5-HT₂ antagonist sarpogrelate ($ED_{50} = 0.04$ and 2.2 mg/kg p.o., respectively).

SOURCE – Welfide.

REFERENCES

1. Kuroita, T. et al. (Welfide Corporation) *Pyrrolidine cpds. and medicinal utilization thereof*. WO 0026186.

2. Fujio, M. et al. *N*-[1-(2-Phenylethyl)pyrrolidin-3-yl]-1-adamantanecarboxamides as novel 5-HT₂ receptor antagonists. Bioorg Med Chem Lett 2000, 10(21): 2457.

*Identified compound **289794** Drug Data Rep 2000, 022(09): 0794.

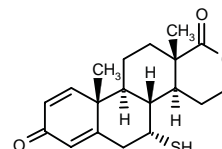
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

TZA-2237*

210903

7α-Mercapto-17-oxa-17a-homoandrost-1,4-diene-3,17a-dione



C₁₉ H₂₄ O₃ S; Mol wt: 332.4650

ACTION – Steroidal aromatase inhibitor devoid of androgenic, estrogenic, progestational and 5α-reductase-inhibitory effects. In a model of hormonally induced benign prostatic hyperplasia (BPH) in dogs, compound at oral doses of 2.5 mg/kg 5 times weekly for 6 months significantly reduced adrenal and prostate weights, significantly decreased intraprostatic estradiol levels and androgen receptor content, and significantly increased intraprostatic dihydrotestosterone compared to control animals. In dogs with spontaneous BPH, treatment with compound was associated with a significant increase in prostatic growth compared to untreated animals, as well as significant increases in serum luteinizing hormone (LH) and testosterone levels. When compound (1 mg/kg/day) was given for over 20 weeks (5 days/week) in combination with the antiandrogen chlormadinone acetate (0.03 mg/kg/day), a significant decrease in intraprostatic estradiol concentrations was observed compared with chlormadinone alone, and a significant decrease in the proportion of smooth muscle. Potentially useful for the treatment of BPH.

SOURCE – Teikoku Hormone.

REFERENCES

1. Koizumi, N. et al. (Teikoku Hormone Manufacturing Co., Ltd.) *Novel 7-substd. oxa-azasteroid cpd*. EP 0663402, JP 1994508897, US 5539127, WO 9407908.

2. Ito, K. et al. *Effects of a new steroidal aromatase inhibitor, TZA-2237, and/or chlormadinone acetate on hormone-induced and spontaneous canine benign prostatic hyperplasia*. Eur J Endocrinol 2000, 143(4): 543.

*Identified compound **210903** (see **209669**) Drug Data Rep 1994, 016(08): 0769.

SOURCE – Sankyo.

REFERENCES

1. Asai, F. and Fujimoto, K. (Sankyo Co., Ltd.) *Compsn. containing diarylalkane deriv. as the active ingredient for treating or preventing pancreatitis*. JP 1998212232, WO 9823271.

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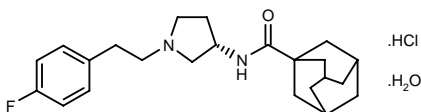
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Y-39241*

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*Identified compound **289794** Drug Data Rep 2000, 022(09): 0794.

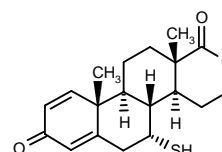
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

TZA-2237*

210903

7α-Mercapto-17-oxa-17a-homoandrost-1,4-diene-3,17a-dione



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SOURCE – Teikoku Hormone.

REFERENCES

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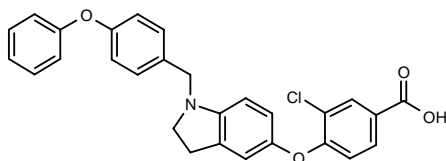
2. Ito, K. et al. *Effects of a new steroidal aromatase inhibitor, TZA-2237, and/or chlormadinone acetate on hormone-induced and spontaneous canine benign prostatic hyperplasia*. Eur J Endocrinol 2000, 143(4): 543.

*Identified compound **210903** (see **209669**) Drug Data Rep 1994, 016(08): 0769.

YM-36117

249132

3-Chloro-4-[1-(4-phenoxybenzyl)-2,3-dihydro-1*H*-indol-5-yloxy]benzoic acid



C28 H22 Cl N O4; Mol wt: 471.9378

ACTION – Steroid 5 α -reductase inhibitor with about 100-fold greater activity than the reference compound Ono-3805 against human enzyme (IC_{50} = 5.3 and 538 nM, respectively). At an oral dose of 100 mg/kg, compound reduced by 44% prostatic concentrations of dehydro-testosterone in rats. Potentially useful for the treatment of benign prostatic hyperplasia (BPH).

SOURCE – Yamanouchi.

REFERENCES

1. Igarashi, S. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Benzoic acid derivs. or their salts*. JP 1995145147.

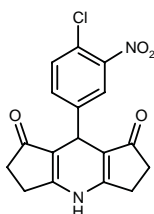
2. Igarashi, S. et al. *A novel class of inhibitors for human and rat steroid 5 α -reductases: Synthesis and biological evaluation of indoline and aniline derivatives. III*. Chem Pharm Bull 2000, 48(11): 1689.

3. Igarashi, S. et al. *Synthesis and 5 α -reductase inhibitory activity of novel indole derivatives*. 16th Symp Med Chem (Nov 27-29, Toyama) 1996, Abst 2-P-38.

TREATMENT OF URINARY INCONTINENCE

294413

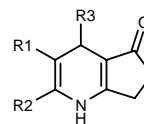
8-(4-Chloro-3-nitrophenyl)-1,2,3,4,5,6,7,8-octahydro-dicyclopenta[*b,e*]pyridine-1,7-dione



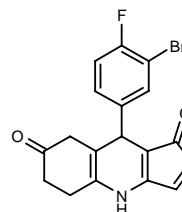
C17 H13 Cl N2 O4; Mol wt: 344.7527

ACTION – Water-soluble potassium channel opener proven to induce a 113% maximal steady-state membrane hyperpolarization relative to the reference compound P-1075 (assigned 100%) and giving an EC_{50} of 0.053 nM in primary cultured guinea pig urinary bladder cells. This compound was also active in reducing stimulated contractions in isolated tissue strips from pig bladders. Its utility for the treatment of urinary incontinence was demonstrated by its ability to inhibit bladder contractions in rats, in which it produced a 30% reduction in the area

under the curve at 0.1 μ mol/kg i.v. The water solubility of the compound at pH 7.4 and 6.5 was 129 nmol/ml. Other exemplified cyclopentanone dihydropyridines are:



Compound	R1	R2	R3	Formula
294417	-COCH2CH2-		3-Br-4-F-Ph	C ₁₇ H ₁₃ BrFNO ₂
294418	-COCH2CH2-		3-CN-Ph	C ₁₈ H ₁₄ N ₂ O ₂
294420	-COCH2CH2-		3-NO2-Ph	C ₁₇ H ₁₄ N ₂ O ₄
294421	-COCH2CH2-		3-Cl-4-F-Ph	C ₁₇ H ₁₃ ClFNO ₂
294423	-COCH2CH2-		3,4-(Cl)2-Ph	C ₁₇ H ₁₃ Cl ₂ NO ₂
294425	-COCH2CH2-		2,1,3-benzoxadiazol-5-yl	C ₁₇ H ₁₃ N ₃ O ₃
294426	-COCH2CH2-		4-F-3-I-Ph	C ₁₇ H ₁₃ FINO ₂
294429	CO2H	Me	3-Br-4-F-Ph	C ₁₆ H ₁₃ BrFNO ₃



294427: C18 H13 Br F N O2

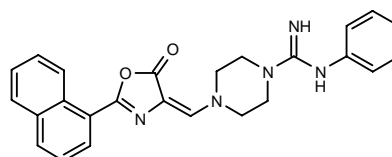
SOURCE – Abbott.

REFERENCES

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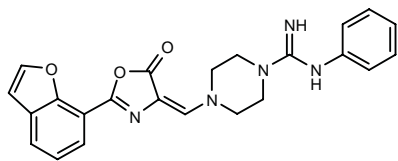
295059

4-[2-(1-Naphthyl)-5-oxo-4,5-dihydrooxazol-4-ylidene-methyl]-*N*-phenylpiperazine-1-carboxamide



C25 H23 N5 O2; Mol wt: 425.4897

ACTION – Selective α_{1B} -adrenoceptor antagonist with potential for the treatment of urinary tract disorders such as incontinence, benign prostatic hypertrophy, prostatitis, detrusor hyperreflexia, overactive bladder, urethritis, cystitis or idiopathic bladder hypersensitivity, as well as for the treatment of male or female sexual dysfunction and pain. Compound exhibited significant antinociceptive activity in the radiant heat assay in neuropathic rats subjected to chronic constriction injury at 60-1000 μ g/kg i.p., and it was also effective in a cold allodynia response assay in neuropathic rats at 300 μ g/kg i.p. In addition, it was found to be considerably less potent than prazosin at lowering blood pressure in normotensive or spontaneously hypertensive rats following i.v. administration, and is thus expected to exhibit fewer side effects than nonselective agents. Another exemplified compound from this series of oxazolone derivatives is:



295060: C23 H21 N5 O3

SOURCE – Roche.

REFERENCES

1. Coffen, D.L. et al. (F. Hoffmann-La Roche AG) *Oxazolone derivs. and their use as α-1 adrenoreceptor modulators*. WO 0055143.

GASTROINTESTINAL DRUGS

TREATMENT OF ESOPHAGEAL DISEASES

ESOMEPRAZOLE MAGNESIUM+

Prop INNM

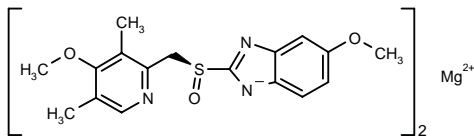
272598

5-Methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinyl-methyl)sulfinyl]-1H-benzimidazole magnesium salt

H-199/18

(–)-Omeprazole magnesium

(S)-Omeprazole magnesium



C34 H36 Mg N6 O6 S2; Mol wt: 713.1314

ACTION – Single-isomer proton pump inhibitor.

INDICATION – Treatment of erosive reflux esophagitis, long-term management of healed esophagitis to prevent relapse, symptomatic treatment of gastroesophageal reflux disease (GERD), and in combination with appropriate antibacterial therapeutic regimens for healing *Helicobacter pylori*-associated duodenal ulcer and preventing relapse of peptic ulcers in patients with *H. pylori*-associated ulcers.

PRESENTATION – Tablets, 20 and 40 mg esomeprazole as magnesium trihydrate.

PROPRIETARY NAME – Nexium (SE).

SOURCE – AstraZeneca.

RECENT REFERENCES

1. Andersson, T. et al. *Esomeprazole 40 mg capsules are bioequivalent when administered intact or as the contents mixed with applesauce*. Clin Drug Invest 2001, 21(1): 67.

2. Andersson, T. et al. *Esomeprazole open capsule mixed with applesauce is bioequivalent to the intact capsule when administered to healthy volunteers*. 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.48.

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6. Genta, R.M. et al. *Safety of long-term treatment with a new PPI, esomeprazole in GERD patients*. Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A16.

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8. Hassan-Alin, M. et al. *Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects*. Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A16.

9. Hassan-Alin, M. et al. *Pharmacokinetics of esomeprazole in healthy subjects*. 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 940.

10. Hasslegren, G. et al. *Pharmacokinetics of esomeprazole are unaltered in the elderly*. 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.47.

11. Johnson, D.A. et al. *Efficacy and safety of esomeprazole as maintenance therapy in GERD patients with healed erosive esophagitis (EE)*. Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A17.

12. Johnson, D.A. et al. *Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: A randomized, double-blind, placebo-controlled study of efficacy and safety*. Am J Gastroenterol 2001, 96(1): 27.

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14. Junghard, O. et al. *The effect of AUC and Cmax of esomeprazole on acid secretion and intragastric pH*. Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A17.

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16. Kahrilas, P.J. et al. *Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: A randomized controlled trial*. Aliment Pharmacol Ther 2000, 14(10): 1249.

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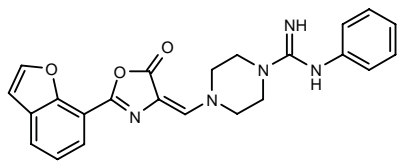
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25. Talley, N.J. et al. *Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: A controlled trial of "on-demand" therapy for 6 months*. Aliment Pharmacol Ther 2001, 15(3): 347.

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27. Thitipheree, S. and Talley, N.J. *Esomeprazole, a new proton pump inhibitor: Pharmacological characteristics and clinical efficacy*. Int J Clin Pract 2000, 54(8): 537.



295060: C23 H21 N5 O3

SOURCE – Roche.

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GASTROINTESTINAL DRUGS

TREATMENT OF ESOPHAGEAL DISEASES

ESOMEPRAZOLE MAGNESIUM⁺

Prop INNM

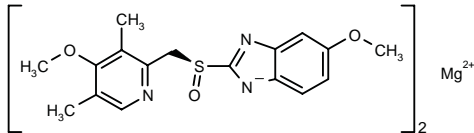
272598

5-Methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinyl-methyl)sulfinyl]-1H-benzimidazole magnesium salt

H-199/18

(–)-Omeprazole magnesium

(S)-Omeprazole magnesium



C34 H36 Mg N6 O6 S2; Mol wt: 713.1314

ACTION – Single-isomer proton pump inhibitor.

INDICATION – Treatment of erosive reflux esophagitis, long-term management of healed esophagitis to prevent relapse, symptomatic treatment of gastroesophageal reflux disease (GERD), and in combination with appropriate antibacterial therapeutic regimens for healing *Helicobacter pylori*-associated duodenal ulcer and preventing relapse of peptic ulcers in patients with *H. pylori*-associated ulcers.

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39. AstraZeneca receives E.U. approval for Nexium. DailyDrugNews.com (Daily Essentials) 2000, July 14.

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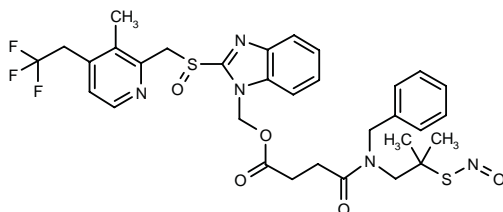
MONOGRAPH – Graul, A. et al. *Esomeprazole magnesium*. Drugs Fut 1999, 24(11): 1178.

*Drug Data Rep 1999, 021(05): 0424.

ANTIULCER DRUGS

294204

N-Benzyl-*N*-[2-methyl-2-(nitrososulfanyl)propyl]-succinamic acid 2-[3-methyl-4-(2,2,2-trifluoroethyl)pyridin-2-ylmethylsulfanyl]benzimidazol-1-ylmethyl ester



C32 H34 F3 N5 O5 S2; Mol wt: 689.7766

ACTION – Proton pump inhibitor, a nitrosylated lansoprazole derivative with improved gastroprotective, anti-*Helicobacter pylori* and antacid properties. The compound significantly inhibited ethanol/HCl-induced gastric ulcer formation in rats at a dose of 200 μ mol/kg by oral gavage.

SOURCE – NitroMed.

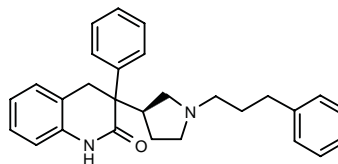
REFERENCES

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AGENTS FOR IRRITABLE BOWEL SYNDROME

294655

3-Phenyl-3-[1-(3-phenylpropyl)pyrrolidin-3(*S*)-yl]-1,2,3,4-tetrahydroquinolin-2-one



C28 H30 N2 O; Mol wt: 410.5580

ACTION – A representative compound from a series of quinoline derivatives active as muscarinic M_3 receptor antagonists, with potential for the treatment of gastrointestinal disorders such as irritable bowel syndrome, functional dyspepsia and spastic colon, as well as CNS disorders such as nausea, vomiting and motion sickness, urinary disorders such as urinary incontinence and pollakiuria, and respiratory disorders such as chronic obstructive pulmonary disease, asthma, pulmonary fibrosis and rhinitis. *In vitro*, compound exhibited pA_2 values of 8.9, 8.1 and 7.0, respectively, when tested for its ability to inhibit carbachol-induced contractions in M_3 -bearing tissues, i.e., guinea pig ileum, urinary bladder and trachea, while giving a pA_2 value of 7.8 in guinea pig left atrium (M_2).

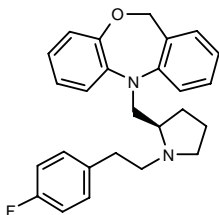
SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

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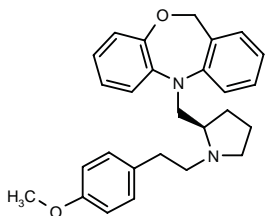
294842

(+)-5-[1-[2-(4-Fluorophenyl)ethyl]pyrrolidin-2(*R*)-ylmethyl]-5,11-dihydrodibenzo[*b,e*][1,4]oxazepine



C26 H27 F N2 O; Mol wt: 402.5103

ACTION – Agent for the treatment of gastrointestinal disorders, particularly irritable bowel syndrome, a calcium channel antagonist with selectivity for the intestinal tract over the heart and devoid of side effects, particularly anticholinergic activity. Compound was shown to inhibit wrap restraint stress (WRS)-induced defecation in rats with an ID₅₀ value of 1.8 mg/kg p.o. (ID₅₀ nicardipine = 6.8 mg/kg p.o.), while showing no hypotensive effects in these animals (ED₂₀ > 1000 mg/kg p.o.; ED₂₀ nicardipine = 4.0 mg/kg p.o.). When tested further in rats, compound exhibited no anticholinergic effects at 300 mg/kg p.o. and did not induce decreases in body temperature at a dose of 100 mg/kg p.o. LD₅₀ > 200 mg/kg i.p. in mice. Another specifically claimed compound from this series of 5,11-dihydrodibenzo[*b,e*][1,4]oxazepine derivatives is:



294844: C27 H30 N2 O2

SOURCE – Ajinomoto.

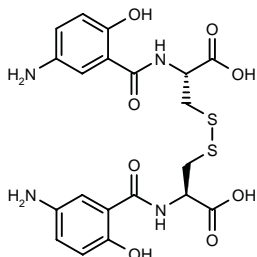
REFERENCES

1. Tanaka, Y. et al. (Ajinomoto Co., Inc.) 5,11-Dihydrodibenzo[*b,e*][1,4]oxazepine derivs. and pharmaceutical compns. containing the same. US 6127361, WO 9733885.

**AGENTS FOR
INFLAMMATORY BOWEL DISEASE****5-ASA-Cys**

295335

N,N'-bis(5-amino-2-hydroxybenzoyl)-L-cystine



C20 H22 N4 O8 S2; Mol wt: 510.5458

ACTION – Colon-specific prodrug of 5-aminosalicylic acid (5-ASA) which is not metabolized and is poorly absorbed in the stomach and in the small intestine. In contrast, compound was microbially activated in the colon to release 5-ASA, with almost complete conversion to 5-ASA at 24 h. The concentration of 5-ASA in the urine was almost 2-fold lower after administration of compound compared to free 5-ASA, indicating low systemic toxicity. Potentially useful for the treatment of inflammatory bowel disease and Crohn's disease.

SOURCES – National Institutes of Health, Bethesda, MD (US); Pusan National University, Pusan (KR); University of Utah, Salt Lake City, UT (US).

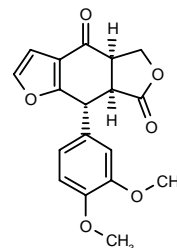
REFERENCES

1. Jung, Y. et al. *Synthesis and in vitro/in vivo evaluation of N,N'-bis(5-aminoasacilic)-L-cystine as a colon-specific prodrug of 5-aminosalicylic acid.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 1176.

**TREATMENT OF LIVER AND BILIARY
TRACT DISORDERS****TA-510***

165401

(±)-8α-(3,4-Dimethoxyphenyl)-4,4α,5,7,7α,8-hexahydrobenzo[1,2-*b*:4,5-*c'*]difuran-4,7-dione



C18 H16 O6; Mol wt: 328.3184

ACTION – Hepatic antiinflammatory agent that is well absorbed (80-100%) following oral administration to rats and dogs. In rats, compound was eliminated mainly via the feces after oral administration and via the bile in bile duct-cannulated animals, with significant biliary reabsorption. Distribution studies indicated that radio-labeled compound accumulated in the liver and kidneys, where the levels of radioactivity after an oral dose were higher than in blood. Compound was extensively metabolized in rats and dogs given an oral dose of 30 mg/kg; the major metabolic pathway was *O*-demethylation followed by glucuronidation. In humans, it was largely metabolized after an oral dose of 200 mg and the major metabolites were glucuronides. Further studies indicated that the compound may be metabolized enantioselectively in humans.

SOURCE – Tanabe Seiyaku.

REFERENCES

1. Iwasaki, T. et al. (Tanabe Seiyaku Co., Ltd.) *Biphenyl derivs.* EP 0386778, JP 1990235884, US 5066669.

2. Kume, T. et al. *Studies on the metabolic fate of TA-510, a hepatic anti-inflammatory agent (I): Blood concentration, distribution and excretion in rats and dogs.* Xenobiotic Metab Dispos 2000, 15(4): 318.

3. Kume, T. et al. *Studies on the metabolic fate of TA-510, a hepatic anti-inflammatory agent (II): Metabolism after oral administration to rats, dogs and human.* Xenobiotic Metab Dispos 2000, 15(4): 327.

4. Kume, T. et al. *Studies on the metabolic fate of TA-510, a hepatic anti-inflammatory agent (III): Identification of TA-510 reductase in human liver.* Xenobiotic Metab Dispos 2000, 15(4): 338.

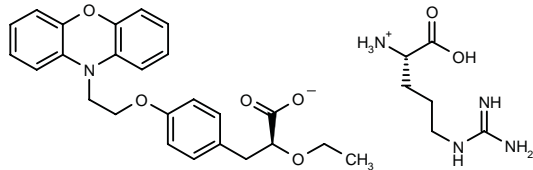
*Identified compound **165401** Drug Data Rep 1991, 013(01): 0045.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

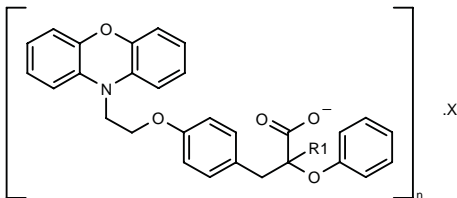
294059

(-)-2(*S*)-Ethoxy-3-[4-[2-(10*H*-phenoxazin-10-yl)ethoxy]-phenyl]propionic acid L-arginine salt



C25 H24 N O5 . C6 H15 N4 O2; Mol wt: 593.6771

ACTION – Agent for the treatment of hyperlipidemia, hypercholesterolemia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance and insulin resistance proven to lower both blood glucose and triglyceride levels by 40% in *db/db* mice when administered at 1 mg/kg/day p.o. x 6 days, and also reported to have the ability to lower total cholesterol and LDL cholesterol levels and increase HDL cholesterol levels. In addition, compound exhibits agonist activity at peroxisome proliferator-activated receptors PPAR α and PPAR γ (9.5- and 12.8-fold activation at 50 and 1 μ M, respectively) and may also inhibit HMG-CoA reductase activity. Other compounds from this series of β -aryl- α -oxysubstituted alkylcarboxylic acid derivatives include the following:



Compound	R1	X	n	Isomer	Formula
294064	H	Mg ⁺²	2	S	2C ₂₅ H ₂₄ NO ₅ .Mg
294065	Me	Na ⁺	1		C ₃₀ H ₂₆ NNaO ₅

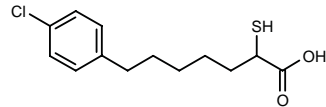
SOURCE – Dr. Reddy's Research Foundation.

REFERENCES

1. Lohray, B.B. et al. (Dr. Reddy's Research Foundation) *Novel tricyclic cpds. and their use in medicine; process for their preparation and pharmaceutical compsn. containing them.* WO 0050414.

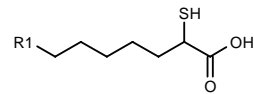
294382

7-(4-Chlorophenyl)-2-sulfanylheptanoic acid



C13 H17 Cl O2 S; Mol wt: 272.7943

ACTION – Antidiabetic agent with antihyperglycemic and PPAR (peroxisome proliferator-activated receptor)-activating activity, shown to significantly lower blood sugar levels in both ddY and KKA^y mice. Other exemplified 2-mercaptocarboxylic acid derivatives are:



Compound	R1	Formula
294384	5-Cl-2-thienyl	C ₁₁ H ₁₅ ClO ₂ S ₂
294385	4-(PhCH ₂ O)-Ph	C ₂₀ H ₂₄ O ₃ S
294387	Ph	C ₁₃ H ₁₈ O ₂ S

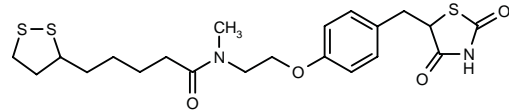
SOURCES – Fuji Chemical; Sankyo.

REFERENCES

1. Kurobe, H. et al. (Sankyo Co., Ltd.;Fuji Chemical Industry Co., Ltd.) *2-Mercapto-carboxylic acid derivs.* JP 2000309573, WO 0050392.

294736

N-[2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenoxy]ethyl]-5-(1,2-dithiolan-3-yl)-*N*-methylpentanamide



C21 H28 N2 O4 S3; Mol wt: 468.6602

ACTION – Peroxisome proliferator-activated receptor PPAR γ activator with potential in the treatment of certain cardiovascular, endocrine, inflammatory, neoplastic, proliferative, neuropsychiatric and viral diseases. *In vitro*, compound was shown to activate PPAR γ in a luciferase reporter gene assay using African green monkey kidney cells, being far more potent than rosiglitazone. In addition, it induced a concentration-dependent inhibition of human keratinocyte proliferation, without inducing cell toxicity, and was shown to be more potent than troglitazone in inhibiting human colon cancer HT-29 and 3T3 L1 fibroblast proliferation. *In vivo*, it reduced serum insulin and glucose levels in insulin-resistant obese Zucker rats at 100 mg/kg/day p.o. x 1 week, being more potent than troglitazone.

2. Kume, T. et al. *Studies on the metabolic fate of TA-510, a hepatic anti-inflammatory agent (I): Blood concentration, distribution and excretion in rats and dogs.* Xenobiotic Metab Dispos 2000, 15(4): 318.

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4. Kume, T. et al. *Studies on the metabolic fate of TA-510, a hepatic anti-inflammatory agent (III): Identification of TA-510 reductase in human liver.* Xenobiotic Metab Dispos 2000, 15(4): 338.

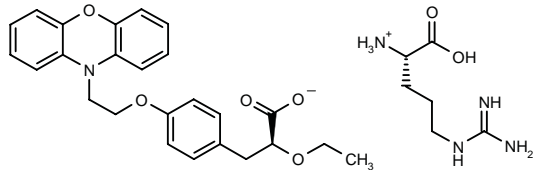
*Identified compound **165401** Drug Data Rep 1991, 013(01): 0045.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

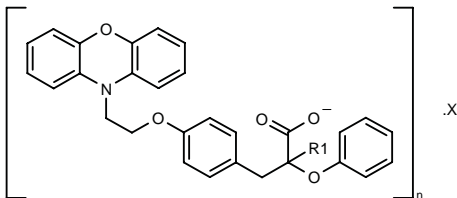
294059

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C25 H24 N O5 . C6 H15 N4 O2; Mol wt: 593.6771

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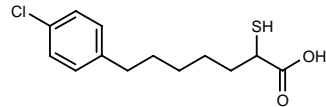
SOURCE – Dr. Reddy's Research Foundation.

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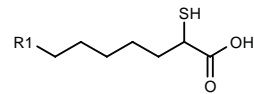
294382

7-(4-Chlorophenyl)-2-sulfanylheptanoic acid



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294387	Ph	C ₁₃ H ₁₈ O ₂ S

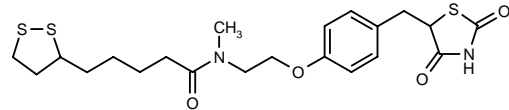
SOURCES – Fuji Chemical; Sankyo.

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294736

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ACTION – Peroxisome proliferator-activated receptor PPAR γ activator with potential in the treatment of certain cardiovascular, endocrine, inflammatory, neoplastic, proliferative, neuropsychiatric and viral diseases. *In vitro*, compound was shown to activate PPAR γ in a luciferase reporter gene assay using African green monkey kidney cells, being far more potent than rosiglitazone. In addition, it induced a concentration-dependent inhibition of human keratinocyte proliferation, without inducing cell toxicity, and was shown to be more potent than troglitazone in inhibiting human colon cancer HT-29 and 3T3 L1 fibroblast proliferation. *In vivo*, it reduced serum insulin and glucose levels in insulin-resistant obese Zucker rats at 100 mg/kg/day p.o. x 1 week, being more potent than troglitazone.

SOURCE – University of Mississippi, Oxford, MS (US).

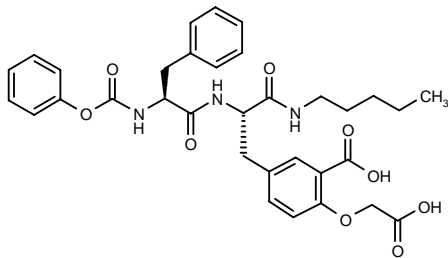
REFERENCES

1. Pershadsingh, H.A. and Avery, M.A. (University of Mississippi) *1,2-Dithiolane derivs.* US 6127394, WO 0053601.

294776

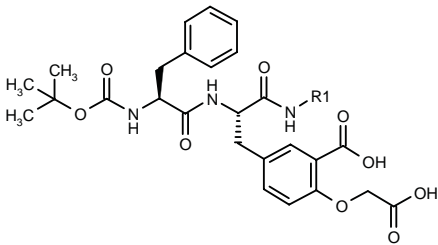
2-(Carboxymethoxy)-5-[3-oxo-3-(pentylamino)-2(*S*)-[2(*S*)-(phenoxycarboxamido)-3-phenylpropionamido]-propyl]benzoic acid

N-(Phenoxycarbonyl)-L-phenylalanyl-3-carboxy-*O*-(carboxymethyl)-*N*-pentyl-L-tyrosinamide



C33 H37 N3 O9; Mol wt: 619.6673

ACTION – Nonpeptide inhibitor of protein-tyrosine-phosphatase PTP1, useful for the treatment or prevention of type 2 diabetes. This compound inhibited the PTP1-induced hydrolysis of *p*-nitrophenol phosphate by 43-97% at 1-100 μ M (K_i = 0.87 μ M). Other exemplified compounds include the following:



Compound	R1	Formula
294777	(CH2)3OH	C ₂₉ H ₃₇ N ₃ O ₁₀
294778	(CH2)4Ph	C ₃₆ H ₄₃ N ₃ O ₉
294779	(CH2)3Ph	C ₃₅ H ₄₁ N ₃ O ₉
294780	(R)-CH(<i>i</i> -Bu)CH2OH	C ₃₂ H ₄₃ N ₃ O ₁₀

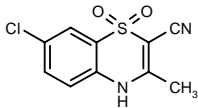
SOURCE – Pharmacia.

REFERENCES

1. Larsen, S.D. et al. (Pharmacia & Upjohn AB) *Inhibitors of protein tyrosine phosphatase.* WO 0053583.

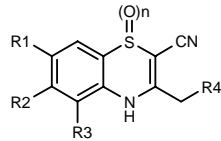
294969

7-Chloro-3-methyl-4*H*-1,4-benzothiazine-2-carbonitrile 1,1-dioxide



C10 H7 Cl N2 O2 S; Mol wt: 254.6963

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal, urogenital and CNS disorders, particularly hyperinsulinemia and diabetes, that acts as an ATP-sensitive potassium (K_{ATP}) channel opener. Other specifically claimed compounds within this series of fused 1,4-thiazine-2-carbonitrile derivatives include the following:



Compound	R1	R2	R3	R4	n	Formula
294970	H	CF3	H	H	2	C ₁₁ H ₇ F ₃ N ₂ O ₂ S
294971	H	CF3	H	H	1	C ₁₁ H ₇ F ₃ N ₂ OS
294972	OMe	H	H	H	2	C ₁₁ H ₁₀ N ₂ O ₃ S
294973	H	F	H	H	2	C ₁₀ H ₇ FN ₂ O ₂ S
294974	H	CF3	H	Et	2	C ₁₃ H ₁₁ F ₃ N ₂ O ₂ S
294975	F	H	F	H	2	C ₁₀ H ₆ F ₂ N ₂ O ₂ S
294976	F	H	H	H	2	C ₁₀ H ₇ FN ₂ O ₂ S

SOURCE – Novo Nordisk.

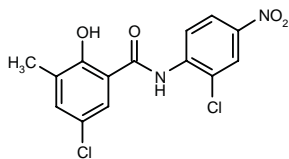
REFERENCES

1. Hansen, H.C. et al. (Novo Nordisk A/S) *Fused 1,4-thiazine-2-carbonitrile derivs., their preparation and use.* WO 0055147.

YM-138552

297082

5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxy-3-methylbenzamide



C14 H10 Cl2 N2 O4; Mol wt: 341.1490

ACTION – Antidiabetic agent, a glucose uptake stimulator proven to increase glucose consumption in murine myoblast muscle C2C12 cells (EC_{50} = 0.07 μ M) and 2-deoxyglucose uptake in mouse skeletal muscle myoblast G8 cells (EC_{50} = 0.19 μ M). In C2C12 cells, compound produced a significant (227% at 15 μ M) and sustained (at least 24 h) increase in glucose transporter Glut4 mRNA levels; in C2C12 cells stably expressing the *myc*-tagged Glut4 protein, compound stimulated Glut4 translocation (EC_{50} = 0.62 μ M) in the absence of insulin, and the addition of insulin was not associated with further stimulation. Selected compound for development for the treatment of type 2 diabetes.

SOURCE – Yamanouchi.

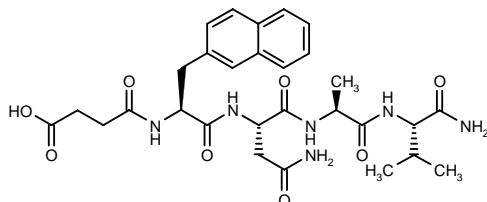
REFERENCES

1. Shimokawa, T. et al. *Glucose uptake stimulator YM-138552 activates gene expression and translocation of glucose transporter isotype.* Drug Dev Res 2000, 51(1): 43.

TREATMENT OF DIABETIC COMPLICATIONS

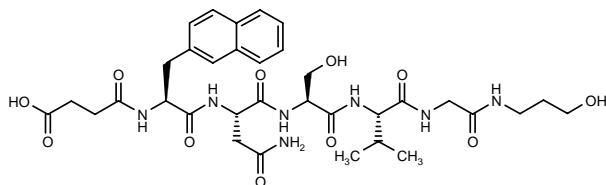
294438

N-(4-Hydroxysuccinyl)-L-3-(2-naphthyl)alanyl-L-asparaginyl-L-alanyl-L-valinamide



C29 H38 N6 O8; Mol wt: 598.6532

ACTION – Agent that is able to interact specifically with the laminin binding site of nidogen, thus competitively inhibiting the interaction between laminin and nidogen ($IC_{50} = 0.085 \mu M$), which is regarded as a key biomolecular mechanism in the synthesis and stabilization of basement membranes. Potentially useful in the treatment of diseases related to increased or unwanted synthesis of basement membranes such as diabetic complications, hepatic fibrosis, atherosclerosis, angiogenesis, cancer, retrolental fibroplasia, rheumatoid arthritis, osteoarthritis, vasculitis, hemangiomas and psoriasis. Another compound from this series of low-molecular-weight peptide derivatives is:



294439: C34 H47 N7 O11

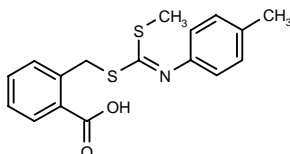
SOURCE – Aventis Pharma.

REFERENCES

1. Stitz, H.U. et al. (Aventis Pharma Deutschland GmbH) *Low molecular weight peptide derivs. as inhibitors of the laminin/nidogen interaction*. EP 1070727, WO 0052051.

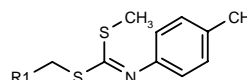
294810

2-[1-(4-Methylphenylimino)-1-(methylsulfanyl)methylsulfanylmethyl]benzoic acid



C17 H17 N O2 S2; Mol wt: 331.4583

ACTION – Antifibrotic agent that acts by blocking the activity of transforming growth factor- β (TGF- β), potentially useful for the treatment of a broad range of fibrotic disorders such as diabetic nephropathy, glomerulonephritis, diabetic retinopathy, type 1 diabetes, hepatic cirrhosis, pulmonary fibrosis, arteriosclerosis, restenosis, pancreatitis and scars. Compound concentration-dependently inhibited TGF- β -induced proteoglycan production in rat fibroblast NRK-49F cells at 5-100 μM (66% inhibition at 25 μM). *In vivo*, it was found to be effective in a rat model of nephritis induced by anti-Thy-1 monoclonal antibody at 150 mg/kg/day p.o. b.i.d. x 1 week. Other exemplified compounds from this series of dithiocarbonimide derivatives include the following:



Compound	R1	Formula
294811	3-quinolyl	C ₁₉ H ₁₈ N ₂ S ₂
294812	2-CO ₂ H-4-Cl-PhCH=CH	C ₁₉ H ₁₈ ClNO ₂ S ₂

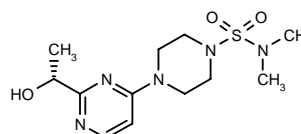
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Yamaga, H. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Dithiocarbonimide derivs.* WO 0055129.

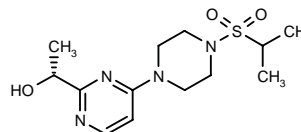
295138

4-[2-[1(*R*)-Hydroxyethyl]pyrimidin-4-yl]-*N,N*-dimethylpiperazine-1-sulfonamide



C12 H21 N5 O3 S; Mol wt: 315.3959

ACTION – Sorbitol dehydrogenase inhibitor ($IC_{50} = 27 \pm 4$ nM) for the treatment of diabetic complications such as diabetic nephropathy, neuropathy and cardiomyopathy. Another specifically claimed compound is:



295139: C13 H22 N4 O3 S

SOURCE – Pfizer.

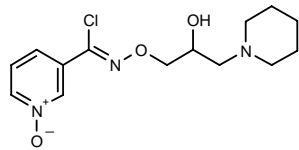
REFERENCES

1. Mylari, B.L. (Pfizer Products Inc.) *Cpds. for treating and preventing diabetic complications*. EP 1041068, JP 2000297075.

BIMOCLOMOL 1-OXIDE

294392

3-[1-Chloro-1-[2-hydroxy-3-(1-piperidinyl)propoxyimino-methyl]pyridine 1-oxide



C14 H20 Cl N3 O3; Mol wt: 313.7830

ACTION – N-Oxide derivative of the known drug bimoclomol that possesses higher potency compared to bimoclomol in improving peripheral motor and sensory nerve conduction velocity deficits in streptozotocin-diabetic rats, and is also able to reduce insulin resistance in Zucker *fa/fa* rats. Particularly suited for the treatment of chronic diabetic complications, especially retinopathy, neuropathy and nephropathy, and for the simultaneous reduction of peripheral insulin resistance, but also for the treatment of nondiabetic pathological insulin resistance.

SOURCE – Biorex Laboratories.

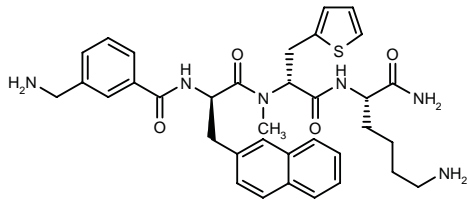
REFERENCES

1. Kürthy, M. et al. (Biorex Kutató és Fejlesztő Rt.) *N*-[2-Hydroxy-3-(1-piperidinyl)propoxy]pyridine-1-oxide-3-carboximidoyl chloride and its use in the treatment of insulin resistance. WO 0050403.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

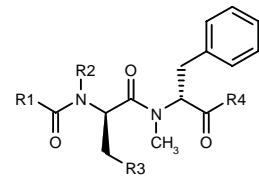
294889

N-[3-(Aminomethyl)benzoyl]-3-(2-naphthyl)-D-alanyl-N-methyl-3-(2-thienyl)-D-alanyl-L-lysineamide

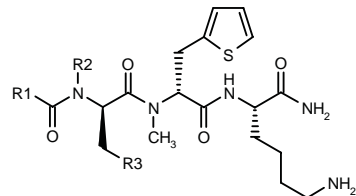


C35 H42 N6 O4 S; Mol wt: 642.8208

ACTION – Growth hormone-releasing agent with a good oral bioavailability and substantially no side effects. It acts *in vitro* directly on the pituitary cells to release growth hormone and is thus potentially useful for the treatment of growth hormone deficiency disorders and for understanding the regulation of growth hormone secretion at the pituitary level. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	Formula
294892	CH=CHCH2-C(Me)2NH2	H	2-Naph	-L-Lys-NH2	C ₃₆ H ₄₈ N ₆ O ₄
294897	(CH2)3-C(Me)2NH2	Me	4-Ph-Ph	NHCH2CH2NH2	C ₃₅ H ₄₇ N ₅ O ₃
294898	(CH2)3-C(Me)2NH2	H	2-Naph	NH(CH2)5NH2	C ₃₅ H ₄₉ N ₅ O ₃
294899	3-(NH2CH2)-Ph	Me	2-Naph	N(Me)CH2-CH2N(Me)2	C ₃₇ H ₄₅ N ₅ O ₃
294902	CH=CHCH2-C(Me)2NH2	Me	2-Naph	-(N6-Ac-N2-Me)-L-Lys-NHMe	C ₄₁ H ₅₆ N ₆ O ₅



Compound	R1	R2	R3	Formula
294893	CH=CHCH2-C(Me)2NH2	H	2-Naph	C ₃₄ H ₄₆ N ₆ O ₄ S
294895	3-(NH2CH2)-Ph	H	4-Ph-Ph	C ₃₇ H ₄₄ N ₆ O ₄ S

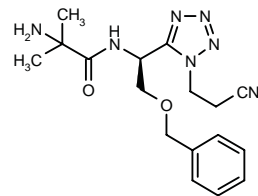
SOURCE – Novo Nordisk.

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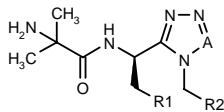
295038

2-Amino-N-[1(S)-[1-(2-cyanoethyl)-1H-tetrazol-5-yl]-2-(benzyloxy)ethyl]-2-methylpropionamide

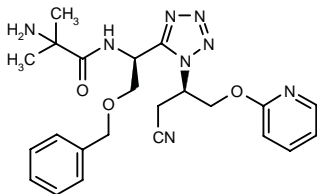


C17 H23 N7 O2; Mol wt: 357.4157

ACTION – Growth hormone secretagogue potentially useful for the treatment of osteoporosis and obesity, and for increasing muscle mass and/or strength. Other specifically claimed heterocyclic aromatic compounds include the following:



Compound	R1	R2	A	Formula
295039	OCH2Ph	CH2OCONHCH2-CH2OC(Me)2OH	N	C ₂₂ H ₃₅ N ₇ O ₆
295040	3-indolyl	2-furyl	C(t-BuS)	C ₂₅ H ₃₂ N ₆ O ₂ S
295041	OCH2Ph	1-(MeSO2)-3-indolyl-CH2	CH	C ₂₆ H ₃₂ N ₆ O ₄ S
295042	OCH2Ph	CH2CH2CONHCH2-CH2OCH2CH2OH	N	C ₂₂ H ₃₅ N ₇ O ₅



295043: C23 H28 N8 O3

SOURCE – Bristol-Myers Squibb.

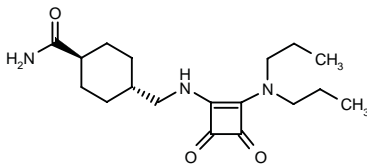
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TREATMENT OF MALE SEXUAL DYSFUNCTION

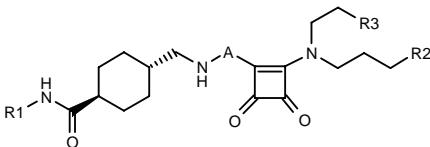
294562

trans-4-[2-(Dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl-aminomethyl]cyclohexanecarboxamide



C18 H29 N3 O3; Mol wt: 335.4451

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor potentially useful for the treatment of benign prostatic hypertrophy, urinary incontinence, male and female sexual dysfunction, pulmonary hypertension, stroke, atherosclerosis, peripheral vascular disorders, asthma, bronchitis, allergic rhinitis, glaucoma and gastrointestinal motility disorders. Other specifically claimed cyclobutene-3,4-dione derivatives include the following:



Compound	R1	R2	R3	A	Formula
294563	cyclopropyl	H	Me	bond	C ₂₁ H ₃₃ N ₃ O ₃
294564	H	Me	H	-CH2-	C ₁₉ H ₃₁ N ₃ O ₃
294565	H	H	Me	-CH2-	C ₁₉ H ₃₁ N ₃ O ₃

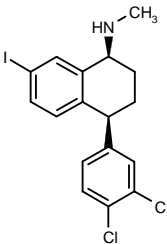
SOURCE – Sanofi-Synthélabo.

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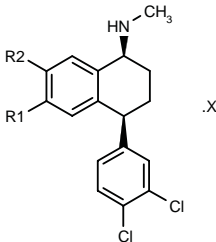
294584

N-[4(S)-(3,4-Dichlorophenyl)-7-iodo-1,2,3,4-tetrahydro-naphthalen-1(S)-yl]-N-methylamine



C17 H16 Cl2 I N; Mol wt: 432.1264

ACTION – Selective inhibitor of 5-HT reuptake potentially useful for the treatment of disorders in which regulation of the monoamine transporter function is implicated including depression, attention deficit hyperactivity disorder, obsessive–compulsive disorder, posttraumatic stress disorder, substance abuse or sexual dysfunction. Preferably, it is indicated for the treatment or prevention of premature ejaculation. Other exemplified 1,2,3,4-tetrahydro-1-naphthalenamine compounds include the following:



Compound	R1	R2	X	Formula
294585	H	SO2N(Me)2		C ₁₉ H ₂₂ Cl ₂ N ₂ O ₂ S
294586	H	SO2NHCH2CH2NH2		C ₁₉ H ₂₃ Cl ₂ N ₃ O ₂ S
294587	H	4-(NH2CO)-1-Pip-SO2		C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃ S
294588	H	2H-1,2,3-triazol-2-yl	HCl	C ₁₉ H ₁₈ Cl ₂ N ₄ .HCl
294589	H	6-NH2-2-Pyr		C ₂₂ H ₂₁ Cl ₂ N ₃
294590	H	SOMe		C ₁₈ H ₁₉ Cl ₂ NOS
294591	H	CH2CH2CONH2	HCl	C ₂₀ H ₂₂ Cl ₂ N ₂ O.HCl
294592	H	NH2		C ₁₇ H ₁₈ Cl ₂ N ₂
294593	(CH2)2SO2NH2	H		C ₁₉ H ₂₂ Cl ₂ N ₂ O ₂ S
294594	CONH2	NHSO2Me	HCl	C ₁₈ H ₂₁ Cl ₂ N ₃ O ₃ S.HCl

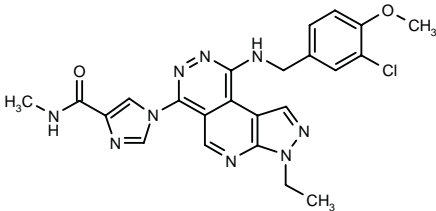
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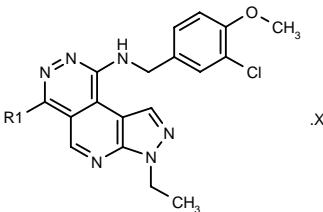
295183

1-[9-(3-Chloro-4-methoxybenzylamino)-3-ethyl-3*H*-pyrazolo[4',3':5,6]pyrido[3,4-*d*]pyridazin-6-yl]-*N*-methyl-1*H*-imidazole-4-carboxamide



C23 H22 Cl N9 O2; Mol wt: 491.9408

ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor for the treatment of sexual dysfunction including erectile dysfunction and female arousal disorder, as well as for the therapy of cardiovascular disorders. Other specifically claimed fused pyridopyridazines are:



Compound	R1	X	Formula
295184	4-(MeNHCO)-1-imidazolyl	MeSO3H	C ₂₃ H ₂₂ ClN ₉ O ₂ .CH ₄ O ₃ S
295186	4-Pyr-CH2NH		C ₂₄ H ₂₃ ClN ₈ O
295187	4-(CH2OH)-1-imidazolyl		C ₂₂ H ₂₁ ClN ₈ O ₂
295189	4-[N(Me)2CH2CH2NHCO]-1-imidazolyl		C ₂₆ H ₂₉ ClN ₁₀ O ₂
295191	4-(1-Me-4-Pip-NHCO)-1-imidazolyl		C ₂₈ H ₃₁ ClN ₁₀ O ₂
295192	4-(1-pyrrolidinyl-CO)-1-imidazolyl		C ₂₆ H ₂₆ ClN ₉ O ₂
295194	4-[2(R)-(MeOCH2)-1-pyrrolidinyl-NHCO]-1-imidazolyl		C ₂₈ H ₃₁ ClN ₁₀ O ₃
295195	4-(CH2CO2H)-1-imidazolyl		C ₂₃ H ₂₁ ClN ₈ O ₃

SOURCE – Bristol-Myers Squibb.

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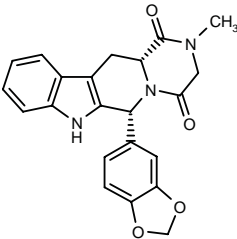
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IC-351

251999

(6*R*,12*aR*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-1,2,3,4,6,7,12,12*a*-octahydropyrazino[2',1':6,1]pyrido[3,4-*b*]-indole-1,4-dione

GF-196960
Cialis™



C22 H19 N3 O4; Mol wt: 389.4091

ACTION – Potent, selective, orally active inhibitor of phosphodiesterase type 5 (PDE5) undergoing phase III clinical studies for the treatment of erectile dysfunction. Results from phase II clinical studies in men with mild to moderate erectile dysfunction showed that compound given daily for 3 weeks (up 100 mg) or on demand (up to 25 mg) was safe and generally well tolerated and improved erectile function and sexual satisfaction.

SOURCES – Icos; Lilly.

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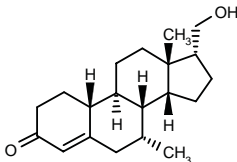
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CONTRACEPTIVES

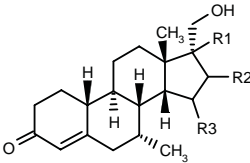
294737

(7α,14β,17α)-17-(Hydroxymethyl)-7-methylestra-4-en-3-one



C20 H30 O2; Mol wt: 302.4550

ACTION – Steroid with androgenic activity that has the configuration 14β,17α, as opposed to the 14α,17β configuration of natural products. Potentially useful in male contraception, alone or combined with a progestagen, and in male or female hormone replacement therapy. Other exemplified androstane derivatives are:



Compound	R1	R2	R3	Formula
294738	H	bond		C ₂₀ H ₂₈ O ₂
294739	F	H	H	C ₂₀ H ₂₉ FO ₂

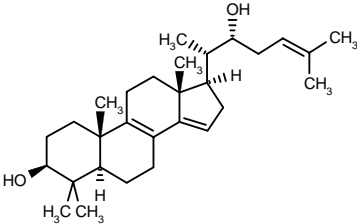
SOURCE – Akzo Nobel.

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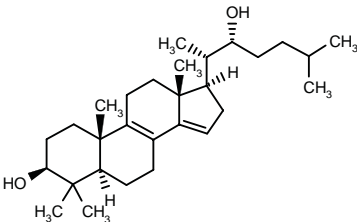
294740

(3β,5α,20S,22R)-4,4-Dimethylcholesta-8,14,24-trien-3,22-diol



C29 H46 O2; Mol wt: 426.6804

ACTION – Potent meiosis inhibitor potentially useful as a male or female contraceptive agent. Another exemplified compound from this series of 22R-hydroxycholesta-8,14-diene derivatives is:



294741: C29 H48 O2

SOURCE – Akzo Nobel.

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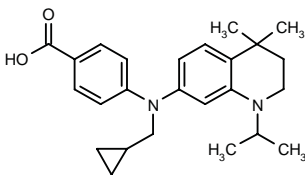
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DERMATOLOGIC DRUGS

MISCELLANEOUS DERMATOLOGIC DRUGS

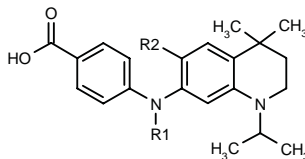
294847

4-[N-(Cyclopropylmethyl)-N-(1-isopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)amino]benzoic acid



C25 H32 N2 O2; Mol wt: 392.5398

ACTION – Selective retinoid X receptor (RXR) agonist with potential in the treatment of skin diseases such as actinic keratoses, acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema and atopic dermatitis, as well as for the treatment of metabolic diseases, hyperproliferative diseases including cancer, and certain ophthalmological and cardiovascular diseases. Compound exhibited EC₅₀ values of 0.1, 3 and 0.2 nM, respectively, for RXR α , RXR β and RXR γ receptors in a transactivation assay, while being inactive at retinoic acid receptors (RARs). Other compounds from this series of amines substituted with a tetrahydroquinolinyl group include the following:



Compound	R1	R2	Formula
294848	Et	H	C ₂₃ H ₃₀ N ₂ O ₂
294849	i-Bu	H	C ₂₅ H ₃₄ N ₂ O ₂
294850	H	Me	C ₂₂ H ₂₈ N ₂ O ₂
294851	Me	Me	C ₂₃ H ₃₀ N ₂ O ₂
294852	Et	Me	C ₂₄ H ₃₂ N ₂ O ₂
294853	Pr	Me	C ₂₅ H ₃₄ N ₂ O ₂

SOURCE – Allergan.

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AMINOLEVULINIC ACID HYDROCHLORIDE*

Prop IINM; USAN

191307

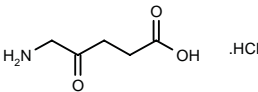
5-Amino-4-oxopentanoic acid hydrochloride

5-Aminolevulinic acid hydrochloride

δ -Aminolevulinic acid hydrochloride

ALA HCl

ALA-PDT



C5 H9 N O3 . Cl H; Mol wt: 167.5910

ACTION – Agent for photodynamic therapy, a metabolic precursor of the photosensitizer protoporphyrin IX.

INDICATION – Treatment of nonhyperkeratotic actinic keratoses of the face and scalp.

PRESENTATION – Single-unit dosage form consisting of a plastic tube containing two ampoules and an applicator tip: one ampoule contains 1.5 ml solution vehicle and the other 354 mg aminolevulinic acid hydrochloride.

PROPRIETARY NAME – Levulan (US).

SOURCES – Berlex (Schering AG); Dusa.

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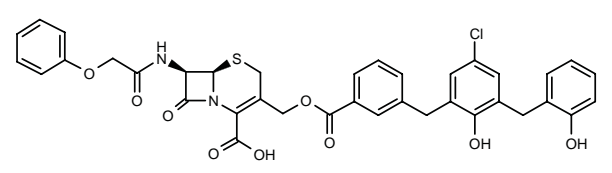
*Identified compound **191307** Drug Data Rep 1993, 015(03): 0223.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

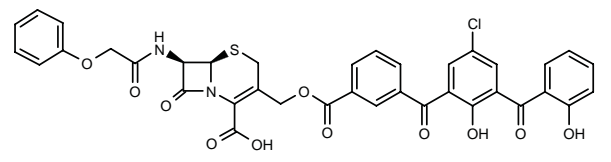
294300

(6*R*,7*R*)-3-[3-[5-Chloro-2-hydroxy-3-(2-hydroxybenzyl)-benzyl]benzoyloxymethyl]-7-(2-phenoxyacetamido)-3-cephem-4-carboxylic acid



C37 H31 Cl N2 O9 S; Mol wt: 715.1759

ACTION– Bifunctional antimicrobial agent that consists of a phloroglucide derivative attached to a cephalosporin. The compound has a broad spectrum of antimicrobial activity including *Staphylococcus aureus* FDA 209P, *S. aureus* 95, *Candida albicans*, *Pseudomona aeruginosa* 1101-75 and *P. aeruginosa* 18S-H. Another exemplified compound is:



294301: C37 H27 Cl N2 O11 S

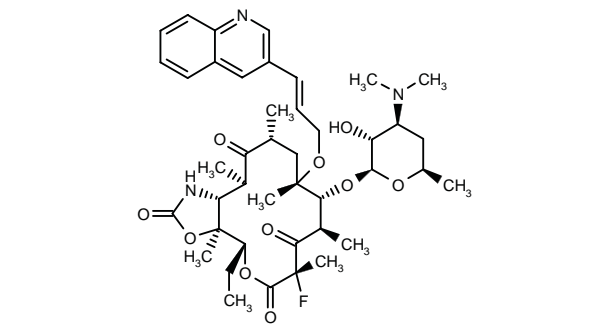
SOURCE – National Science Council, Taiwan, Taipei (TW).

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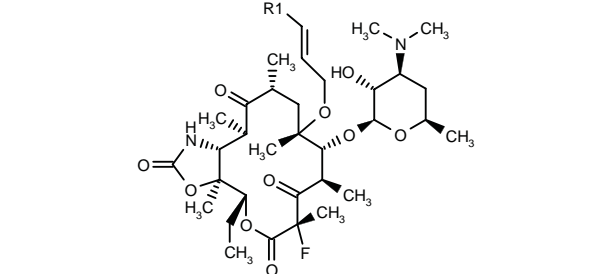
294675

11-Amino-11-deoxy-3-des(hexopyranosyloxy)-2-fluoro-3-oxo-6-*O*-[3-(3-quinoliny)-2(*E*)-propenyl]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C42 H58 F N3 O10; Mol wt: 783.9292

ACTION – Ketolide antibiotic with potent activity against several strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Haemophilus influenzae*, etc. Other exemplified 2-halo-6-*O*-substituted ketolides are:



Compound	R1	Formula
294676	Ph	C ₃₉ H ₅₇ FN ₂ O ₁₀
294677	2-quinoxaliny	C ₄₁ H ₅₇ FN ₄ O ₁₀

13. Piacquadio, D. et al. *Efficacy and safety of photodynamic therapy with topical 5-aminolevulinic acid*. 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P26.

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15. Robinson, D.J. et al. *Improved response of plaque psoriasis after multiple treatments with topical 5-aminolaevulinic acid photodynamic therapy*. Acta Dermato-Venereol 1999, 79(6): 451.

16. Van den Boogert, J. et al. *Kinetics, localization, and mechanism of 5-aminolevulinic acid-induced porphyrin accumulation in normal and Barrett's-like rat esophagus*. Lasers Surg Med 1999, 24(1): 3.

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18. *Berlex now marketing Levulan Kerastick photodynamic therapy in U.S.* DailyDrugNews.com (Daily Essentials) 2000, Dec 13.

19. *Draxis seeks approval of Levulan PDT in Canada*. DailyDrugNews.com (Daily Essentials) 2000, March 31.

20. *Dusa receives FDA approvable letter for Levulan NDA*. DailyDrugNews.com (Daily Essentials) 1999, June 30.

21. *Dusa receives first approval of Levulan PDT for treatment of actinic keratoses*. DailyDrugNews.com (Daily Essentials) 1999, Dec 10.

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23. *Dusa updates Levulan PDT development*. DailyDrugNews.com (Daily Essentials) 1999, Oct 18.

24. *FDA advisory panel review of Levulan to be rescheduled*. DailyDrugNews.com (Daily Essentials) 1999, May 24.

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MONOGRAPH – Pento, J.T. *δ-Aminolevulinic acid*. Drugs Fut 1997, 22(1): 0011.

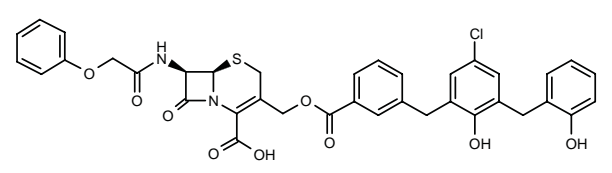
*Identified compound **191307** Drug Data Rep 1993, 015(03): 0223.

ANTIINFECTIVE THERAPY

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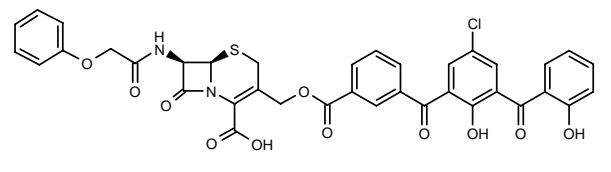
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(6*R*,7*R*)-3-[3-[5-Chloro-2-hydroxy-3-(2-hydroxybenzyl)-benzyl]benzoyloxymethyl]-7-(2-phenoxyacetamido)-3-cephem-4-carboxylic acid



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294301: C37 H27 Cl N2 O11 S

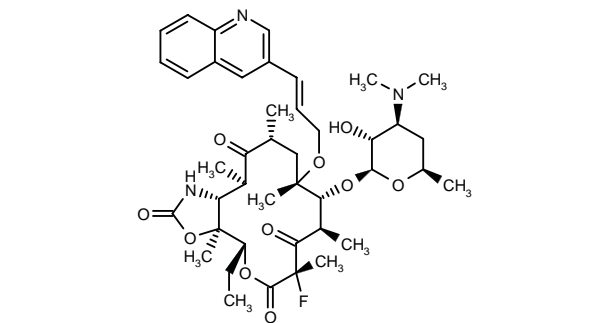
SOURCE – National Science Council, Taiwan, Taipei (TW).

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1. Hwu, J.R. et al. (National Science Council, Taiwan) *Phloroglucide derivs. and their pharmaceutical use*. US 6121255.

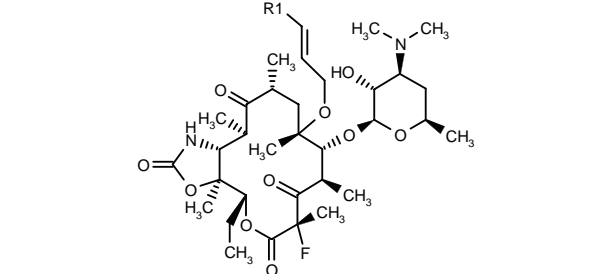
294675

11-Amino-11-deoxy-3-des(hexopyranosyloxy)-2-fluoro-3-oxo-6-*O*-[3-(3-quinoliny)-2(*E*)-propenyl]erythromycin A 11-*N*,12-*O*-cyclic carbamate



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ACTION – Ketolide antibiotic with potent activity against several strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Haemophilus influenzae*, etc. Other exemplified 2-halo-6-*O*-substituted ketolides are:



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294677	2-quinoxaliny	C ₄₁ H ₅₇ FN ₄ O ₁₀

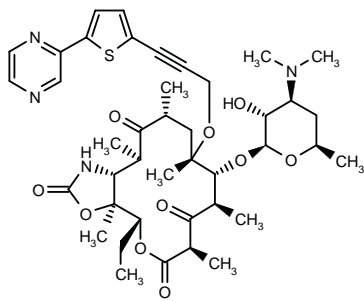
SOURCE – Abbott.

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1. Phan, L.T. et al. (Abbott Laboratories Inc.) 2-Halo-6-O-substd. ketolide derivs. US 6124269.

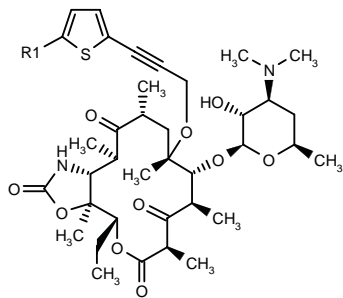
295095

11-Amino-11-deoxy-3-des(hexopyranosyloxy)-3-oxo-6-O-[3-[5-(2-pyrazinyl)thien-2-yl]-2-propynyl]erythromycin A 11-N,12-O-cyclic carbamate



C41 H56 N4 O10 S; Mol wt: 796.9774

ACTION – Macrolide antibiotic with good antibacterial activity against a range of Gram-positive bacteria and some Gram-negative pathogens including *Staphylococcus aureus* A5177 (MIC = 0.05 µg/ml vs. 3.1 µg/ml for erythromycin A), *Staphylococcus epidermidis* 3519 (MIC = 0.05 µg/ml vs. 0.39 µg/ml for erythromycin A), *Enterococcus faecium* ATCC8043 (MIC = 0.02 µg/ml vs. 0.05 µg/ml for erythromycin A), *Streptococcus bovis* A5169 (MIC = 0.005 µg/ml or less vs. 0.02 µg/ml for erythromycin A), *Streptococcus pyogenes* EES61 (MIC = 0.02 µg/ml vs. 0.05 µg/ml for erythromycin A), *Escherichia coli* SS (MIC = 0.2 µg/ml vs. 0.78 µg/ml for erythromycin A) and *Streptococcus pneumoniae* ATCC6303 (MIC = 0.015 µg/ml vs. 0.06 µg/ml for erythromycin A). Other exemplified 6-O-substituted erythromycin derivatives include the following:



Compound	R1	Formula
295096	2-pyrimidinyl	C ₄₁ H ₅₆ N ₄ O ₁₀ S
295097	2-furyl	C ₄₁ H ₅₆ N ₂ O ₁₁ S
295098	3-thienyl	C ₄₁ H ₅₆ N ₂ O ₁₀ S ₂
295099	5-thiazolyl	C ₄₀ H ₅₅ N ₃ O ₁₀ S ₂
295100	1-Me-2-imidazolyl	C ₄₁ H ₅₈ N ₄ O ₁₀ S

SOURCE – Abbott.

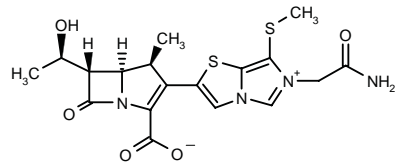
REFERENCES

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CP-5068

293397

(1*S*,5*R*,6*S*)-2-[6-(Carbamoylmethyl)-7-(methylsulfanyl)-imidazo[5,1-*b*]thiazol-6-ium-2-yl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate



C18 H20 N4 O5 S2; Mol wt: 436.5110

ACTION – Carbapenem antibiotic with strong antibacterial activity against Gram-positive bacteria including resistant pathogens. The antibacterial activity of compound against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MRSA) was comparable to vancomycin (MIC = 0.008 and 4 µg/ml, respectively, for compound and 0.5 and 2 µg/ml, respectively, for vancomycin), whereas it was more active than vancomycin and meropenem against both penicillin-sensitive and -resistant *Streptococcus pneumoniae* (PRSP; MIC < 0.004 and 0.031 µg/ml, respectively). The potent activity of compound against MRSA and PRSP is attributed to its high affinity for PBP2' from MRSA (IC₅₀ = 1-5 µg/ml) and for both PBP2B and PBP1A from PRSP. *In vivo*, compound showed better therapeutic efficacy than the reference antibiotics ceftriaxone, cefotaxime and vancomycin against experimental systemic infections caused by PRSP (ED₅₀ = 0.16 mg/kg/day s.c.) and vancomycin, imipenem and linezolid against MRSA (PD₅₀ = 0.08-0.45 mg/day s.c.). Compound was also active against experimental pneumonia caused by PRSP in mice and experimental meningitis in rabbits caused by PRSP.

SOURCE – Meiji Seika.

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2. Ida, T. et al. CP5068, a new carbapenem: In vitro and in vivo activities against MRSA. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1237.

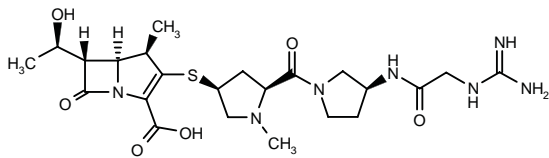
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4. Ubukata, K. et al. CP 5068, a new carbapenem: In vitro and in vivo activities against penicillin-resistant *Streptococcus pneumoniae*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1238.

R-115685

293388

(1*R*,5*S*,6*S*)-2-[5(*S*)-[3(*S*)-(2-Guanidinoacetamido)pyrrolidin-1-ylcarbonyl]-1-methylpyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C23 H35 N7 O6 S; Mol wt: 537.6385

ACTION – Carbapenem antibiotic with potent and broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* and imipenem-resistant *Pseudomonas aeruginosa*. The activity of compound is generally comparable to that of imipenem against Gram-positive bacteria and to that of meropenem against Gram-negative bacteria. In addition, an additive or synergistic activity against MRSA and *P. aeruginosa* was observed when compound was combined with vancomycin or amikacin. Compound showed up to 16-fold higher activity as compared to imipenem or meropenem against resistant mutants of *P. aeruginosa* and was stable to hydrolysis by a variety of β -lactamases, except metallo- β -lactamases produced by, e.g., *Bacteroides fragilis*. Compound is stable to dehydropeptidase I (DHP-I) hydrolysis and appears to be associated with less nephrotoxicity than meropenem. *In vivo*, it displayed excellent efficacy against a number of murine infections including systemic infections caused by *S. aureus*, *Staphylococcus epidermidis*, *S. pneumoniae*, Enterobacteriaceae and *P. aeruginosa*, as well as against pneumonia induced by penicillin-resistant *P. aeruginosa*, subcutaneous infections caused by methicillin-susceptible or -resistant *S. aureus*, and urinary tract infections caused by *Escherichia coli*, *Citrobacter freundii*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Proteus mirabilis* and *P. aeruginosa*. In general, its activity was comparable to that of imipenem/cilastatin and better than that of meropenem, ceftriaxone, ampicillin and ceftazidime. Pharmacokinetic and safety studies showed a longer half-life for the compound compared to available carbapenems, no general toxicity in rats after single doses (up to 2000 mg/kg i.v.) or repeated doses (up to 1000 mg/kg i.v. over 4 days), a low liability for neurotoxicity in rats and nephrotoxicity in rabbits, and no genotoxicity.

SOURCE – Sankyo.

REFERENCES

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2. Kawamoto, I. et al. (Sankyo Co., Ltd.) *Crystalline 1-methylcarbapenem cpds.* WO 0102401.
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7. Ohya, S. et al. *R-115685, a novel parenteral carbapenem: In vivo antibacterial activity.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1232.
8. Shibayama, T. et al. *R-115685, a novel parenteral carbapenem: Pharmacokinetics and metabolism in laboratory animals.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1233.

WAP-2607B2

294815

ACTION – Antibiotic isolated from *Flavobacterium* sp. WAP-2607 (FERM P-17284), proven active against Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). *In vitro*, compound exhibited MIC values of 1.56, 0.78 and 1.56 μ g/ml against MRSA JCM8702, *Staphylococcus epidermidis* ATCC12228 and *Bacillus subtilis* ATCC6633, respectively, and MIC values of 0.20, 0.10 and 0.20 μ g/ml against the same strains in the presence of 10% serum; MIC values against *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* were > 100 μ g/ml. *In vivo*, it completely protected mice inoculated with *S. aureus* JCM8702 from death when given at 1.0 mg/kg s.c., being more effective than vancomycin at 10 mg/kg s.c. No signs of acute toxicity were observed following administration of up to 250 mg/kg i.p. to mice. Another compound isolated from the same source is:

WAP-2607B1
[294816]

SOURCE – Wakamoto.

REFERENCES

1. Katoh, A. et al. (Wakamoto Pharmaceutical Co., Ltd.) *Antibiotic WAP-2607B, process for producing the same and antibacterial agents.* WO 0055186.

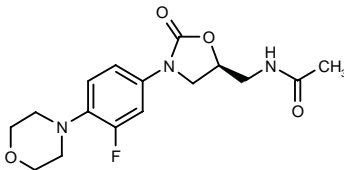
ANTIBACTERIAL DRUGS

LINEZOLID
Prop INN: USAN

224298

N-[3-[3-Fluoro-4-(morpholin-4-yl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide

PNU-100766
U-100766*



C16 H20 F N3 O4; Mol wt: 337.3540

ACTION – Synthetic oxazolidinone antibacterial agent.

INDICATION – Treatment of adult infections associated with vancomycin-resistant *Enterococcus faecium* including bloodstream infections, as well as nosocomial pneumonia, skin and skin structure infections and community-acquired pneumonia caused by other susceptible microorganisms.

PRESENTATION – Tablets, 400 and 600 mg; oral suspension as dry granules/powder for reconstitution, equivalent to 100 mg/5 ml; solution for i.v. infusion (2 mg/ml), 200 mg/100 ml, 400 mg/200 ml and 600 mg/300 ml.

PROPRIETARY NAME – Zyvox (US).

SOURCE – Pharmacia.

RECENT REFERENCES

1. Ballow, C.H. et al. *Multicenter evaluation of linezolid antimicrobial activity in North America (NA)*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-2303.

2. Bassetti, M, et al. *Linezolid (LZD) treatment of prosthetic hip infections due to methicillin-resistant Staphylococcus aureus (MRSA)*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst M-2231.

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16. Cammarata, S.K. et al. *Incidence of Clostridium difficile-related complications during clinical trials of linezolid, an oxazolidinone*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst K-947.

17. Cammarata, S.K. et al. *Linezolid eradicates common pathogens in community-acquired pneumonia*. Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP239.

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35. Hendershot, P.E. et al. *Pharmacokinetics of linezolid in patients with liver diseases*. 5th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 26-28, Seville) 2000, Abst 8.17.

36. Hyatt, J.M. et al. *Safety and efficacy of linezolid (PNU-100766) in eradication of nasal Staphylococcus aureus*. 5th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 26-28, Seville) 2000, Abst 8.26.

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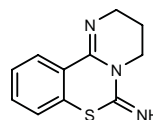
MONOGRAPH – Lizondo, J. et al. *Linezolid*. Drugs Fut 1996, 21(11): 1116.

*See U-100592 Drug Data Rep 1996, 018(01): 0070.

PD-404182

295176

3,4-Dihydro-2H-pyrimido[1,2-c][1,3]benzothiazin-6-imine



C11 H11 N3 S; Mol wt: 217.2949

ACTION – An inhibitor of 2-dehydro-3-deoxyphospho-octonate aldolase, also known as 3-deoxy-D-manno-octulosonic acid 8-phosphate synthase or KDO-8-P synthase, potentially useful for combating drug-resistant bacteria. Despite its strong inhibitory activity against KDO-8-P synthase ($K_i = 26$ nM), compound exhibited only weak antibacterial activity, probably due to its poor bio-availability and rapid metabolism. Studies are in progress to improve the bioavailability of the compound.

SOURCE – Pfizer.

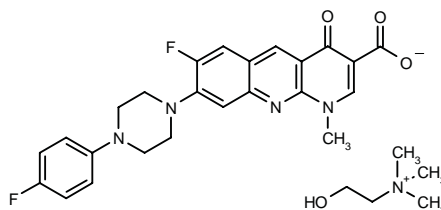
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RP-60556A

291830

7-Fluoro-8-[4-(4-fluorophenyl)piperazin-1-yl]-1-methyl-4-oxo-1,4-dihydrobenzo[b][1,8]naphthyridine-3-carboxylic acid 2-hydroxy-*N,N,N*-trimethyl-1-ethanaminium salt



C24 H19 F2 N4 O3 . C5 H14 N O; Mol wt: 553.6067

ACTION – Topical antibacterial agent, the choline salt of a benzo[*b*]naphthyridone with strong activity against Gram-positive cocci including multiresistant strains of staphylococci, streptococci and enterococci, and without crossresistance to quinolones, β -lactams, mupirocin and fusidic acid. Compound showed comparable activity against quinolone-sensitive and -resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*. In contrast to mupirocin which was mainly bacteriostatic against *S. aureus* and *Staphylococcus epidermidis*, compound exhibited bactericidal activity at concentrations 1-4 times the MIC. The topical formulation of compound (1% active compound) showed comparable activity to a 2% fusidic acid formulation and was equally bacteriostatic against quinolone-sensitive and -resistant *S. aureus*. Results in a guinea pig model of skin infection caused by multidrug-resistant *S. aureus* indicated comparable activity for topical compound (2% active compound) and mupirocin (2%).

SOURCE – Aventis Pharma.

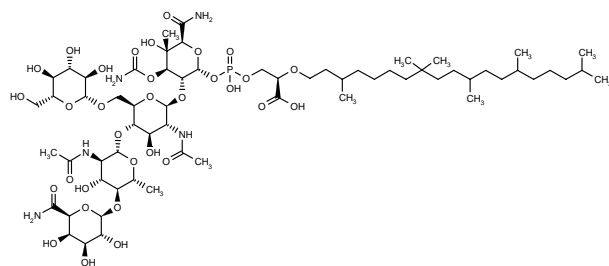
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TS-0511²

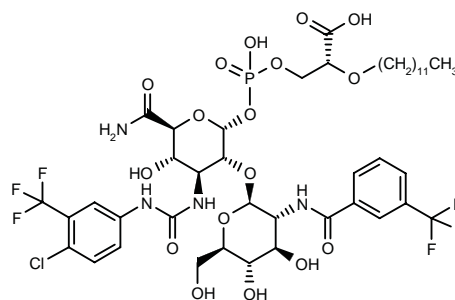
295288

β -D-Galactopyranosyluronamide-(1 \rightarrow 4)-O-(2-acetamido-2,6-dideoxy- β -D-glucopyranosyl)-(1 \rightarrow 4)-O-[2-acetamido-2-deoxy-6-O-(β -D-glucopyranosyl)- β -D-glucopyranosyl]-(1 \rightarrow 2)-1-O-[[2(*R*)-carboxy-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)ethoxy](hydroxy)phosphoryl]-3-O-carbamoyl-4-C-methyl- α -D-glucopyranuronamide

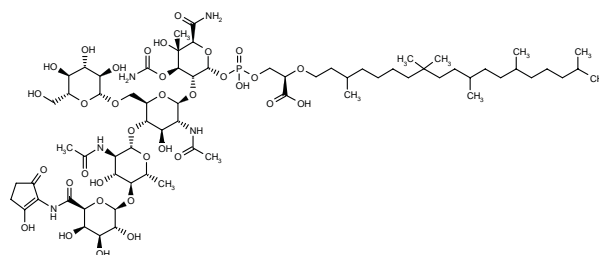


C64 H114 N5 O32 P; Mol wt: 1496.5820

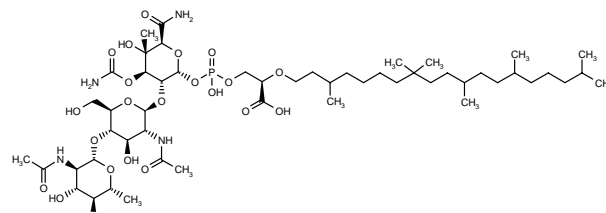
ACTION – Antibacterial agent, a moenomycin analogue active against Gram-positive bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Enterococcus faecalis* (MIC = 0.08, 0.16, 0.16 μ g/ml, respectively), as well as against vancomycin-resistant strains of *E. faecalis* and *Enterococcus faecium* (MIC = 0.25 and 0.39 μ g/ml, respectively). Compound showed comparable bactericidal activity to moenomycin against *S. epidermidis* and, like moenomycin, it inhibited peptidoglycan synthesis in *Escherichia coli* (IC₅₀ = 8.6-87 nM for compound vs. 15.6-31 nM for moenomycin). Other related compounds are:



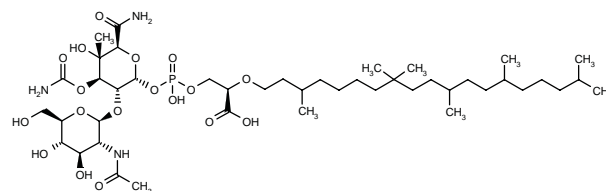
TS-30663 [280007]:*¹⁻³ C43 H58 Cl F6 N4 O17 P



TS-0510 [295285]:² C69 H118 N5 O34 P



TS-0512 [295291]:² C52 H95 N4 O22 P



TS-0514 [295293]:² C44 H82 N3 O18 P

SOURCE – Advanced Medicine.

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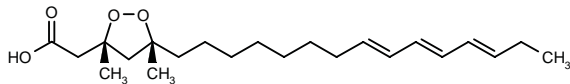
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*Identified compound **280007** (see **280003**) Drug Data Rep 2000, 022(01): 0057.

ANTIFUNGAL AGENTS

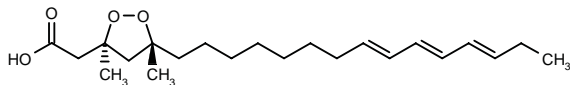
293913

2-[3(R),5(R)-Dimethyl-5-[8(E),10(E),12(E)-pentadeca-trienyl]-1,2-dioxolan-3-yl]acetic acid



C22 H36 O4; Mol wt: 364.5224

ACTION – Antifungal agent extracted from a marine sponge, proven to inhibit the growth of *Candida albicans* with an MIC of 3.1 µg/ml. Another natural product extracted from a marine invertebrate with significant activity against *C. albicans* is:



293914: C22 H36 O4

SOURCES – Harbor Branch Oceanographic Institution; MycoLogics.

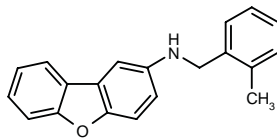
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ANTIVIRAL DRUGS

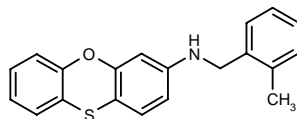
293941

N-(Dibenzo[*b,d*]furan-2-yl)-*N*-(2-methylbenzyl)amine



C20 H17 N O; Mol wt: 287.3603

ACTION – Antiviral agent active against herpes simplex virus type 1 (HSV-1; EC₅₀ = 0.84 µM) and able to inhibit β-galactosidase activity in HSV-infected Vero cells. Compound showed modest activity against human cytomegalovirus (EC₅₀ = 0.8-1.5 µM) and low cytotoxicity (TC₅₀ > 100 µM). Another tricyclic compound is:



293942: C20 H17 N O S

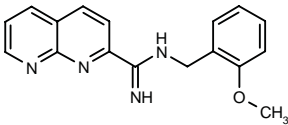
SOURCE – Pfizer.

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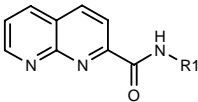
294104

N-(2-Methoxybenzyl)-1,8-naphthyridine-2-carboxamidine



C17 H16 N4 O; Mol wt: 292.3404

ACTION – Antiviral agent for the treatment of herpesvirus and hepatitis virus infections, particularly hepatitis C virus (HCV). Antiviral potency was tested in a bovine viral diarrhea virus (BVDV) assay, which is used as a surrogate to evaluate potential anti-HCV agents due to its functional homology with HCV, where it exhibited an IC₅₀ value of about 0.33 µM, while showing low cytotoxicity in uninfected cells (CC₅₀ > 63.2 µM). Other exemplified compounds from this series of [1,8]naphthyridine derivatives include the following:



Compound	R1	Formula
294105	2-F-PhCH2	C ₁₆ H ₁₂ FN ₃ O
294106	3-NO2-Ph	C ₁₅ H ₁₀ N ₄ O ₃
294107	4-MeO-PhCH2	C ₁₇ H ₁₅ N ₃ O ₂
294109	2,4,6-(MeO)3-PhCH2	C ₁₉ H ₁₉ N ₃ O ₄

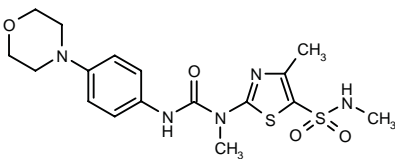
SOURCE – BioChem Pharma.

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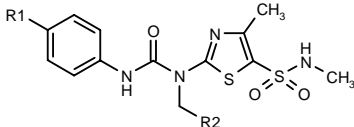
294711

N,4-Dimethyl-2-[*N*-methyl-*N*'-[4-(4-morpholinyl)phenyl]-ureido]thiazole-5-sulfonamide



C17 H23 N5 O4 S2; Mol wt: 425.5317

ACTION – Antiviral agent for the treatment of infections caused by herpesviruses, particularly herpes simplex virus (HSV), with IC₅₀ values of 0.5 and 1.5 μM against HSV-1 F/Vero and HSV-2 G/Vero strains, respectively, compared to IC₅₀ values of 1 and 3 μM, respectively, for aciclovir. Compound also exhibited antiviral activity *in vivo* in infected mice, with an ED₅₀ value of 30-40 mg/kg p.o. Other exemplified compounds from this series of thiazolyl urea derivatives include the following:



Compound	R1	R2	Formula
294712	OEt	CH2N(Me)2	C ₁₈ H ₂₇ N ₅ O ₄ S ₂
294713	1-pyrrolidinyI	H	C ₁₇ H ₂₃ N ₅ O ₃ S ₂
294714	Ph	H	C ₁₉ H ₂₀ N ₄ O ₃ S ₂

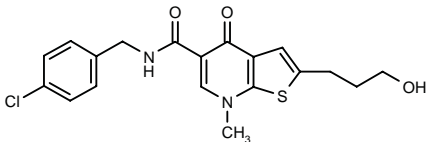
SOURCE – Bayer.

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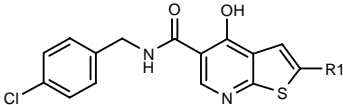
294759

N-(4-Chlorobenzyl)-2-(3-hydroxypropyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide

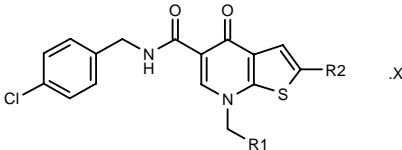


C19 H19 Cl N2 O3 S; Mol wt: 390.8891

ACTION – Antiviral agent, particularly active against herpesviruses. It was found to inhibit human cytomegalovirus (HCMV), herpes simplex virus (HSV) and varicella-zoster virus (VZV) polymerases with respective IC₅₀ values of 0.4, 0.45 and 0.46 μM. Other exemplified 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamides include the following:



Compound	R1	Formula
294762	ethynyl-CH2OH	C ₁₈ H ₁₃ ClN ₂ O ₃ S
294766	CH2CH2CH2OH	C ₁₈ H ₁₇ ClN ₂ O ₃ S



Compound	R1	R2	X	Formula
294767	CH2OH	ethynyl-CH2OH		C ₂₀ H ₁₇ ClN ₂ O ₄ S
294769	CH2N(Et)2	ethynyl-CH2OH	HCl	C ₂₄ H ₂₆ ClN ₃ O ₃ S.HCl
294771	H	4-morpholinyl-CH2		C ₂₁ H ₂₂ ClN ₃ O ₃ S

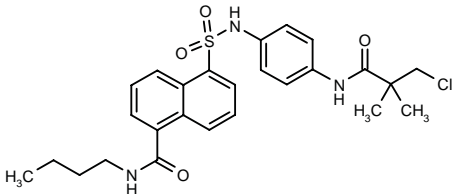
SOURCE – Pharmacia.

REFERENCES

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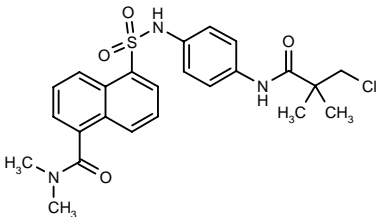
294908

N-Butyl-5-[*N*-(4-(3-chloro-2,2-dimethylpropionamido)-phenyl)sulfamoyl]naphthalene-1-carboxamide



C26 H30 Cl N3 O4 S; Mol wt: 516.0590

ACTION – Antiviral sulfonamide with activity against human cytomegalovirus (HCMV). Particularly indicated for the prophylaxis of HCMV infections in AIDS patients, neonates, infants and transplant patients, and for the treatment of acute HCMV infections in pregnant women. Another exemplified compound is:



294909: C24 H26 Cl N3 O4 S

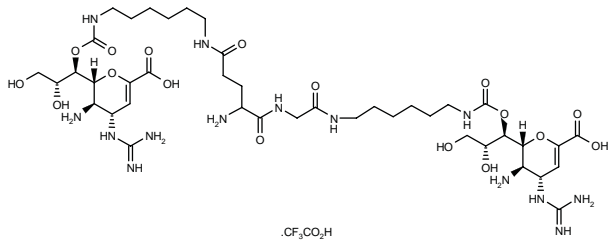
SOURCE – Bayer.

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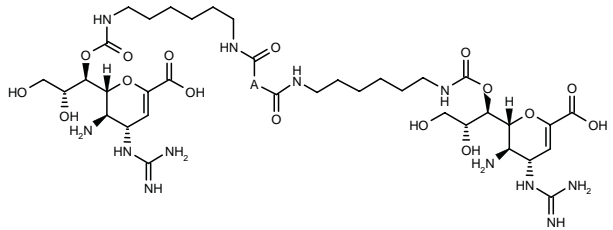
294933

6(*R*),6'(*R*)-[17-Amino-1,2(*R*),33(*R*),34-tetrahydroxy-5,14,18,21,30-pentaoxo-4,31-dioxa-6,13,19,22,29-penta-azatetratriacontane-3(*R*),32(*R*)-diyl]bis[5(*R*)-amino-4(*S*)-guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic acid] tri-fluoroacetate



C41 H72 N14 O17 . C2 H F3 O2; Mol wt: 1147.1230

ACTION – Antiviral agent, a potent inhibitor of influenza virus neuraminidase proven to inhibit the replication of influenza A/Victoria/3/75 B010 in a standard CPE assay with an EC₅₀ value in the range 0.0004-0.002 µg/ml, being more potent than zanamivir (EC₅₀ = 0.009 µg/ml), while showing low cytotoxicity (CC₅₀ > 0.1 µg/ml). Other compounds from this series of dimeric derivatives include the following:



Compound	A	Formula
294934	-NH(CH2)4NH-	C ₄₀ H ₇₂ N ₁₄ O ₁₆
294935	-CH2N(CH2CO2H)CH2CH2N(CH2CO2H)CH2-	C ₄₄ H ₇₆ N ₁₄ O ₂₀

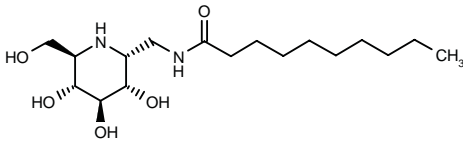
SOURCE – Biota Scientific Management.

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295238

N-[3(*S*),4(*S*),5(*S*)-Trihydroxy-6(*R*)-(hydroxymethyl)-piperidin-2(*R*)-ylmethyl]decanamide



C17 H34 N2 O5; Mol wt: 346.4646

ACTION – Antiviral agent for the treatment of hepatitis B virus (HBV) and hepatitis C virus (HCV) that acts as a glycosylation inhibitor. A representative compound from a series of substituted piperidine derivatives.

SOURCE – CSIRO, Clayton (AU).

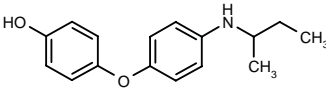
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PD-0084430

293384

4-[4-(1-Methylpropylamino)phenoxy]phenol



C16 H19 N O2; Mol wt: 257.3311

ACTION – Antiviral agent proven to inhibit the replication of human cytomegalovirus (HCMV; EC₅₀ = 0.4-0.6 µM against HCMV strains RC256 and AD169) with similar potency to ganciclovir (EC₅₀ = 0.2-1 µM) and low cytotoxicity (TC₅₀ = 95 µM in HFF cells). Compound is effective against strains of HCMV resistant to ganciclovir, and like ganciclovir, it acts at an early phase in the virus life cycle. Pharmacokinetic studies in mice showed that after oral administration, it is rapidly metabolized and converted to the glucuronide form.

SOURCE – Pfizer.

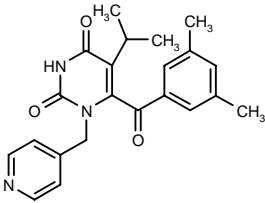
REFERENCES

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AIDS MEDICINES

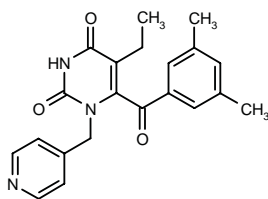
294544

6-(3,5-Dimethylbenzoyl)-5-isopropyl-1-(4-pyridylmethyl)-pyrimidine-2,4(1*H*,3*H*)-dione



C22 H23 N3 O3; Mol wt: 377.4417

ACTION – Antiviral agent with potent activity against both wild-type and mutant HIV. It inhibited HIV-1-induced cytopathic effect in MT-4 cells (EC₅₀ = 0.0026 µg/ml), while showing low cytotoxicity to uninfected MT-4 cells (CC₅₀ = 22.6 µg/ml; selectivity index = 8,600). The compound was also active against the HIV-1 mutant Y181C (EC₅₀ = 0.005-0.014 µM). Another exemplified pyrimidine-2,4-dione derivative is:



294545: C21 H21 N3 O3

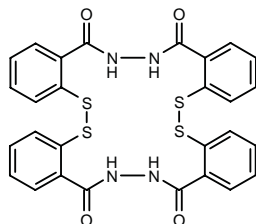
SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

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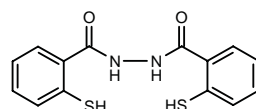
294773

11,12,13,14,25,26,27,28-Octahydrotetrabenzo[*c,i,m,s*]-[1,2,11,12,6,7,16,17]tetrathiatetraazacycloicosine-11,14,25,28-tetraone

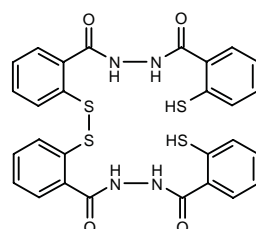


C28 H20 N4 O4 S4; Mol wt: 604.7540

ACTION – A representative compound from a series of mercaptosalicylhydrazides with HIV-1 integrase-inhibitory activity in the presence of both Mn^{2+} (IC_{50} = 2.4 and 7.2 μM , respectively, for 3'-processing and strand-transfer activities in preassembly assays, and 5 and 5 μM , respectively, in postassembly assays) and Mg^{2+} (IC_{50} = 11 and 11 μM , respectively, for 3'-processing and strand-transfer activities in preassembly assays, and 7 and 5 μM , respectively, in postassembly assays), unlike prior integrase inhibitors which are relatively inactivated by Mg^{2+} . Reported to be 300-fold less cytotoxic than other known salicylhydrazides, and to have no detectable effect on other retroviral targets such as reverse transcriptase, protease and virus attachment. It also exhibits no detectable activity against human topoisomerase I at concentrations that effectively inhibit integrase. Other exemplified compounds include the following:



294774: C14 H12 N2 O2 S2



294775: C28 H22 N4 O4 S4

SOURCE – National Institutes of Health, Bethesda, MD (US).

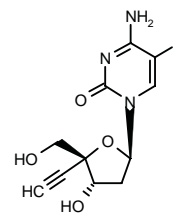
REFERENCES

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4'-E-d5FC^{1,3,4}

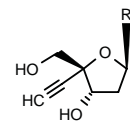
296701

2'-Deoxy-5-fluoro-4'-C-ethynylcytidine



C11 H12 F N3 O4; Mol wt: 269.2308

ACTION – Antiviral agent for AIDS, a nucleoside with potent activity against both wild-type (EC_{50} = 30 nM in MT-4 cells) and multidrug-resistant HIV strains (EC_{50} = 9 nM in HeLa cells). Compound exhibited low cytotoxicity against uninfected cells, giving a selectivity index > 3,000. Other 4'-substituted nucleoside analogues are:



Compound	R1	Formula
4'-E-dA [296709]¹⁻⁴	adenin-9-yl	C ₁₂ H ₁₃ N ₅ O ₃
4'-E-dDAP [296711]¹⁻⁴	2,6-(NH ₂) ₂ -purin-9-yl	C ₁₂ H ₁₄ N ₆ O ₃
4'-E-dG [296713]^{1,3,4}	guanin-9-yl	C ₁₂ H ₁₃ N ₅ O ₄
4'-E-dC [299463]¹⁻⁴	cytosin-1-yl	C ₁₁ H ₁₃ N ₃ O ₄

SOURCE – Yamasa Shoyu.

REFERENCES

1. Ohru, H. et al. (Yamasa Shoyu Co., Ltd.) *4'-C-Ethynyl purine nucleosides*. WO 0069876, WO 0069877.
2. Kodama, E. et al. *4'-Ethynyl nucleoside analogs: Potent inhibitors active against multi-drug-resistant HIV variants in vitro*. 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 305.
3. Ohru, H. et al. *Development of structurally new nucleosides highly active against multi-drug-resistant HIV with low cytotoxicity*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 1P-01.
4. Ohru, H. et al. *Synthesis of 4'-C-ethynyl-β-D-arabino- and 4'-C-ethynyl-2'-deoxy-beta-D-ribo-pentofuranosylpyrimidines and -purines and evaluation of their anti-HIV activity*. J Med Chem 2000, 43(23): 4516.

PHOSPHAZID*

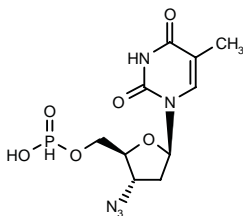
201671

3'-Azido-3'-deoxy thymidine 5'-(hydrogen phosphonate)

Azidothymidine phosphonate

Nicavir

phAZT



C10 H14 N5 O6 P; Mol wt: 331.2236

ACTION – Antiviral agent for AIDS, a nucleoside analogue reverse transcriptase inhibitor with a similar *in vitro* activity and efficacy profile to zidovudine (AZT). Preclinical and clinical studies demonstrated that compound has the same antiretroviral activity as AZT but significantly less toxicity. Moreover, in patients with intolerance to AZT, replacement of AZT therapy with compound showed no serious adverse events, indicating that it can successfully substitute for AZT in such patients. A triple antiretroviral regimen where compound was given in association with nevirapine and didanosine resulted in a median decrease in viral load of 1.6 log₁₀ cells/ml and over 60% of patients had HIV RNA below 400 cells/ml. In addition, a significant increase in CD4 cell counts and in the ratio CD4 to CD8 cells was seen with the triple regimen, and it appeared to be well tolerated.

SOURCE – Russian Academy of Sciences, Moscow (RU).

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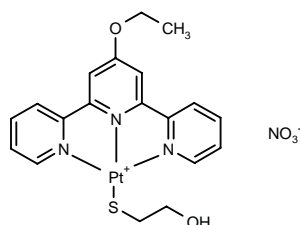
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*Identified compound **201671** Drug Data Rep 1994, 016(01): 0099.

TREATMENT OF PROTOZOAL DISEASES

294108(SP-4-2)-(4'-Ethoxy-2,2':6',2''-terpyridine-κN¹,κN^{1''})[2-(sulfanyl-κS)ethanolato]platinum(1+) nitrate

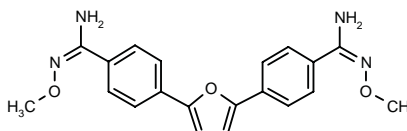
C19 H20 N3 O2 Pt S . N O3; Mol wt: 611.5360

ACTION – Antiparasitic agent active against *Leishmania donovani*, *Trypanosoma cruzi* and *Trypanosoma brucei*, as demonstrated *in vitro* by EC₅₀ values of < 1, < 0.1 and 0.03 µg/ml, respectively. *In vivo* activity was also observed when tested in mice challenged with *L. donovani* or *T. brucei rhodesiense* at a dose of 50 mg/kg/day i.p. x 5 days. In addition, it irreversibly inactivates the reduced form of human thioredoxin reductase (IC₅₀ = 200 nM) and may therefore have potential for the treatment of rheumatoid arthritis.

SOURCE – Isis Innovation.

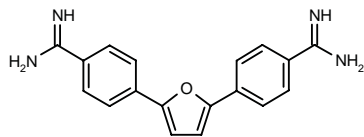
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DB-289*,2-13**246096**4,4'-(Furan-2,5-diyl)bis(*N*-methoxybenzamidine)

C20 H20 N4 O3; Mol wt: 364.4030

ACTION – Antimicrobial agent, a prodrug of **DB-75** that is effective both after oral and i.v. administration against *Pneumocystis carinii* infection in immunosuppressed rats. Compound is undergoing phase I evaluation for the treatment of the opportunistic *P. carinii* infection in immunosuppressed patients. It was found to be transported efficiently across the blood–brain barrier in mice and thus may be potentially useful against brain parasitic infections such as cerebral trypanosomiasis.



DB-75 [278245]^{1,4-8,14}: C₁₈ H₁₆ N₄ O

DB-75 is also being studied for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*.

SOURCES – Georgia State University, Atlanta, GA (US); Immtech; University of North Carolina, Chapel Hill, NC (US).

REFERENCES

1. Boykin, D.W. et al. (Georgia State University; University of North Carolina; Auburn University) *Furan derivs. for inhibiting Pneumocystis carinii pneuminia, Giardia lamblia and Cryptosporidium parvum*. WO 9615126.
2. Hall, J.E. et al. (Georgia State University;University of North Carolina) *Benzamidoxime prodrugs as antipneumocystic agents*. US 5843980.
3. Hall, J.E. et al. (University of North Carolina;Georgia State University) *Benzamidoxime prodrugs as antipneumocystic agents*. EP 0861071, JP 2000500469, US 5723495, WO 9717949.
4. Boykin, D.W. et al. *Anti-Pneumocystis activity of bis-amidoximes and bis-O-alkylamidoximes prodrugs*. Bioorg Med Chem Lett 1996, 6(24): 3017.
5. Del Poeta, M. et al. *In vitro antifungal activities of a series of dication-substituted carbazoles, furans, and benzimidazoles*. Antimicrob Agents Chemother 1998, 42(10): 2503.
6. Trendler, K.L. et al. *Quantification of the prodrug DB289 and an active metabolite, DB75, in rat and monkey plasma using SPE, liquid chromatography and electrospray ionization tandem mass spectrometry*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 4012.
7. Zhou, L. et al. *Metabolism of the O-methylamidoxime prodrug of the novel antimicrobial agent 2,5-bis(4-amidinophenyl)furan*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 4113.
8. Zong, J. et al. *Brain uptake of the antimicrobial agent 2,5-bis(4-amidinophenyl)furan and its prodrug by in situ mouse brain perfusion*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2101.
9. *DB-289 development on track —Immtech to file IND in July*. DailyDrugNews.com (Daily Essentials) 2000, May 16.
10. *Immtech begins DB-289 human trials for opportunistic infection*. DailyDrugNews.com (Daily Essentials) 2000, Oct 17.
11. *Immtech International receives SBIR grant for DB-289*. DailyDrugNews.com (Daily Essentials) 2000, Sept 18.
12. *Immtech scales up production of DB-289; initiation of phase I testing later this year*. DailyDrugNews.com (Daily Essentials) 2000, March 9.
13. *Immtech's DB-289 proves effective against African sleeping sickness*. DailyDrugNews.com (Daily Essentials) 2000, June 2.
14. *Immtech and Tufts studying new drug for common water-borne human parasites*. DailyDrugNew.com (Daily Essentials) 2000, May 3.

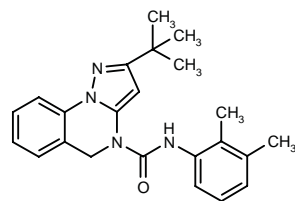
*Identified compound **246096** Drug Data Rep 1997, 019(03): 0259.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

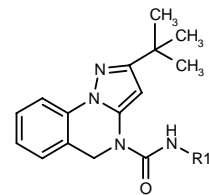
294211

2-*tert*-Butyl-*N*-(2,3-dimethylphenyl)pyrazolo[1,5-*a*]-quinazoline-4(5*H*)-carboxamide



C₂₃ H₂₆ N₄ O; Mol wt: 374.4854

ACTION – Antiinflammatory agent that inhibits the release of IL-1 and TNF and is particularly useful for the treatment of chronic inflammatory diseases. Other specifically claimed polycyclo heterocyclic compounds are:



Compound	R1	Formula
294212	3-Cl-2,4-(MeO)2-Ph	C ₂₃ H ₂₅ ClN ₄ O ₃
294213	2-Me-PhCH2	C ₂₃ H ₂₆ N ₄ O
294214	4-Cl-Ph	C ₂₁ H ₂₁ ClN ₄ O
294216	1-indanyl	C ₂₄ H ₂₆ N ₄ O
294218	2-indanyl	C ₂₄ H ₂₆ N ₄ O
294221	5-indanyl	C ₂₄ H ₂₆ N ₄ O
294222	1,3-benzodioxol-5-yl	C ₂₂ H ₂₂ N ₄ O ₃

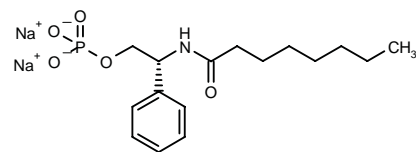
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Cirillo, P.F. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Polycyclo heterocyclic derivs. as antiinflammatory agents*. WO 0050425.

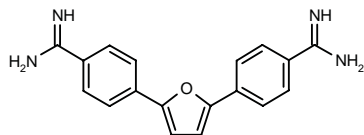
294334

N-[1(*R*)-Phenyl-2-phosphonoxyethyl]octanamide disodium salt



C₁₆ H₂₄ N Na₂ O₅ P ; Mol wt: 387.3216

ACTION – Antimicrobial agent, a prodrug of **DB-75** that is effective both after oral and i.v. administration against *Pneumocystis carinii* infection in immunosuppressed rats. Compound is undergoing phase I evaluation for the treatment of the opportunistic *P. carinii* infection in immunosuppressed patients. It was found to be transported efficiently across the blood–brain barrier in mice and thus may be potentially useful against brain parasitic infections such as cerebral trypanosomiasis.



DB-75 [278245]^{1,4-8,14}: C₁₈ H₁₆ N₄ O

DB-75 is also being studied for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*.

SOURCES – Georgia State University, Atlanta, GA (US); Immtech; University of North Carolina, Chapel Hill, NC (US).

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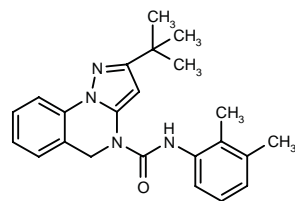
*Identified compound **246096** Drug Data Rep 1997, 019(03): 0259.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

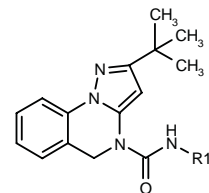
294211

2-*tert*-Butyl-*N*-(2,3-dimethylphenyl)pyrazolo[1,5-*a*]-quinazoline-4(5*H*)-carboxamide



C₂₃ H₂₆ N₄ O; Mol wt: 374.4854

ACTION – Antiinflammatory agent that inhibits the release of IL-1 and TNF and is particularly useful for the treatment of chronic inflammatory diseases. Other specifically claimed polycyclo heterocyclic compounds are:



Compound	R1	Formula
294212	3-Cl-2,4-(MeO)2-Ph	C ₂₃ H ₂₅ ClN ₄ O ₃
294213	2-Me-PhCH2	C ₂₃ H ₂₆ N ₄ O
294214	4-Cl-Ph	C ₂₁ H ₂₁ ClN ₄ O
294216	1-indanyl	C ₂₄ H ₂₆ N ₄ O
294218	2-indanyl	C ₂₄ H ₂₆ N ₄ O
294221	5-indanyl	C ₂₄ H ₂₆ N ₄ O
294222	1,3-benzodioxol-5-yl	C ₂₂ H ₂₂ N ₄ O ₃

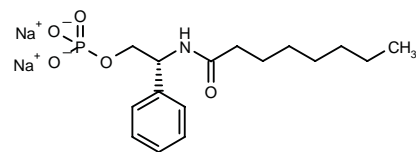
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Cirillo, P.F. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Polycyclo heterocyclic derivs. as antiinflammatory agents*. WO 0050425.

294334

N-[1(*R*)-Phenyl-2-phosphonoxyethyl]octanamide disodium salt



C₁₆ H₂₄ N Na₂ O₅ P ; Mol wt: 387.3216

ACTION – A representative compound from a series of phosphoric acid derivatives that inhibit the production of TNF- α . This compound inhibited lipopolysaccharide-induced TNF- α production in mice (ED_{50} = 2.6 mg/kg i.v.) and is indicated for treating rheumatoid arthritis, ulcerative colitis, Crohn’s disease, hepatitis, sepsis, hemorrhagic shock, multiple sclerosis, infarction, diabetes, etc.

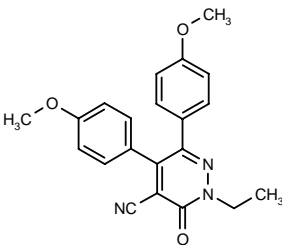
SOURCE – Ono.

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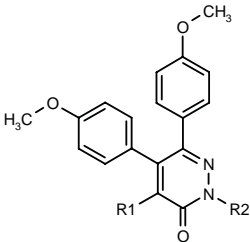
294390

2-Ethyl-5,6-bis(4-methoxyphenyl)-3-oxo-2,3-dihydro-pyridazine-4-carbonitrile



C21 H19 N3 O3; Mol wt: 361.3991

ACTION – IL-1 β production inhibitor (IC_{50} = 0.40 μ M for inhibition of lipopolysaccharide-stimulated IL-1 β production in HL-60 cells), potentially useful for the treatment of inflammatory and autoimmune diseases such as rheumatoid arthritis, osteoporosis, sepsis, inflammatory bowel syndrome, etc. Other exemplified pyridazin-3-one derivatives include the following:



Compound	R1	R2	Formula
294391	CN	cyclopropyl-CH2	C ₂₃ H ₂₁ N ₃ O ₃
294393	CONH2	cyclopropyl-CH2	C ₂₃ H ₂₃ N ₃ O ₄
294394	CN	cyclopentyl-CH2	C ₂₅ H ₂₅ N ₃ O ₃
294395	CO2Et	i-Pr	C ₂₄ H ₂₆ N ₂ O ₅
294396	CO2Et	CH2Ph	C ₂₆ H ₂₆ N ₂ O ₅
294397	1,3-dioxo-2-isoindolinyl-CH2	i-Bu	C ₃₁ H ₂₉ N ₃ O ₅

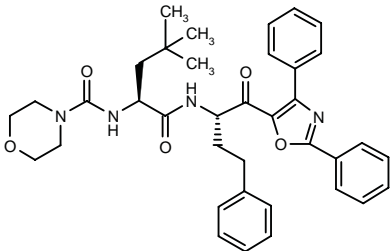
SOURCE – Kowa.

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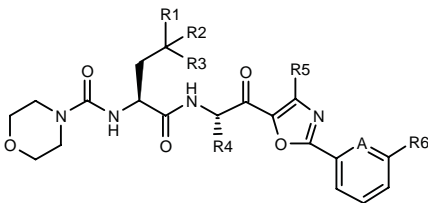
294431

N-[1(S)-[N-[1(S)-(2,4-Diphenyloxazol-5-ylcarbonyl)-3-phenylpropyl]carbamoyl]-3,3-dimethylbutyl]morpholine-4-carboxamide



C37 H42 N4 O5; Mol wt: 622.7618

ACTION – Reversible and selective inhibitor of cathepsin S that inhibits antigen presentation and antigen-specific immune responses, and is therefore useful for the therapy of autoimmune diseases such as rheumatoid arthritis. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
294432	-(CH2)5-	H	H	CH2CH2Ph	Ph	H	CH	C ₃₉ H ₄₄ N ₄ O ₅
294433	Me	H	Me	H	Ph	H	CH	C ₂₈ H ₃₂ N ₄ O ₅
294434	-(CH2)5-	H	H	H	Ph	H	CH	C ₃₁ H ₃₆ N ₄ O ₅
294435	Me	Me	Me	H	Ph	H	CH	C ₂₉ H ₃₄ N ₄ O ₅
294436	Me	H	Me	CH2CH2Ph	H	OCH2Ph	CH	C ₃₇ H ₄₂ N ₄ O ₆
294437	-(CH2)5-	H	H	CH2CH2Ph	i-Bu	H	N	C ₃₆ H ₄₇ N ₅ O ₅

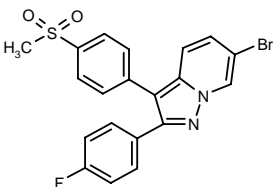
SOURCE – Boehringer Ingelheim.

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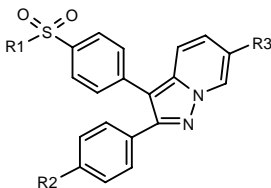
294463

6-Bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-pyrazolo[1,5-a]pyridine



C20 H14 Br F N2 O2 S; Mol wt: 445.3106

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor that exhibited IC₅₀ values of 5 and > 100,000 nM for inhibition of human COX-2 and COX-1, respectively. Particularly useful for the treatment of chronic and acute pain, fever and inflammation. Other compounds from this series of pyrazolo[1,5-*a*]pyridine derivatives are:



Compound	R1	R2	R3	Formula
294465	Me	F	CN	C ₂₁ H ₁₄ FN ₃ O ₂ S
294466	NH2	OEt	Cl	C ₂₁ H ₁₈ ClN ₃ O ₃ S
294467	NH2	H	Cl	C ₁₉ H ₁₄ ClN ₃ O ₂ S

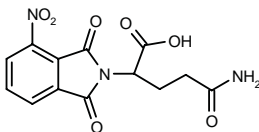
SOURCE – GlaxoSmithKline.

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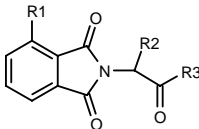
294978

2-(4-Nitro-1,3-dioxo-2,3-dihydro-1 *H*-isoindol-2-yl)glutaramic acid



C13 H11 N3 O7; Mol wt: 321.2439

ACTION – An inhibitor of the production of TNF- α and other inflammatory cytokines such as IL-1, IL-6 and IL-12, with potential for the treatment of inflammatory and autoimmune diseases, cancer and undesirable angiogenesis. Other specifically claimed compounds from this series of substituted 1-oxo and 1,3-dioxoisindolines are:



Compound	R1	R2	R3	Formula
294979	NO2	CO2H	OH	C ₁₁ H ₆ N ₂ O ₈
294980	Me	CO2H	OH	C ₁₂ H ₉ NO ₆
294981	NO2	CH2CH2CO2H	NH2	C ₁₃ H ₁₁ N ₃ O ₇
294982	Me	CH2CH2CONH2	OH	C ₁₄ H ₁₄ N ₂ O ₅
294985	NO2	CH(Me)CONH2	OH	C ₁₃ H ₁₁ N ₃ O ₇
294986	NH2	CH2CONH2	OH	C ₁₂ H ₁₁ N ₃ O ₅
294989	NH2	CH2CH2CONH2	OH	C ₁₂ H ₁₁ N ₃ O ₅

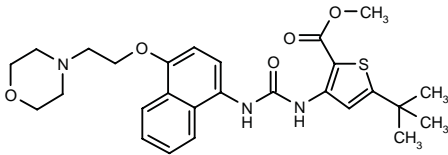
SOURCE – Celgene.

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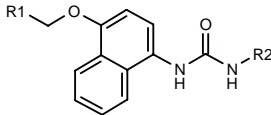
295066

5-*tert*-Butyl-3-[3-[4-[2-(4-morpholinyl)ethoxy]naphthalen-1-yl]ureido]thiophene-2-carboxylic acid methyl ester



C27 H33 N3 O5 S; Mol wt: 511.6397

ACTION – An inhibitor of the release of inflammatory cytokines such as IL-1 and TNF with potential for the treatment of inflammatory and autoimmune diseases, osteoporosis, Alzheimer's disease, acute and chronic pain, stroke, myocardial infarction, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses, hemodialysis and enterocolitis. Other specifically claimed aromatic heterocyclic compounds include the following:



Compound	R1	R2	Formula
295069	1-oxo-4-thio-morpholinyl-CH2	2-(CO2Me)-5-t-Bu-3-thienyl	C ₂₇ H ₃₃ N ₃ O ₅ S ₂
295070	4-THP-CH2	3-(CO2Me)-5-t-Bu-2-thienyl	C ₂₈ H ₃₄ N ₂ O ₅ S
295071	1-imidazolyl-CH2	2-(CO2Me)-5-t-Bu-3-thienyl	C ₂₆ H ₂₈ N ₄ O ₄ S
295073	4-morpholinyl-CH2	1-Me-2-(CO2Me)-5-t-Bu-3-pyrrolyl	C ₂₈ H ₃₆ N ₄ O ₅
295074	4-THP-CH2	2-(CO2Me)-5-t-Bu-3-pyrrolyl	C ₂₈ H ₃₆ N ₃ O ₅
295075	4-Pyr	2-(CO2Me)-5-t-Bu-3-pyrrolyl	C ₂₇ H ₂₈ N ₄ O ₄

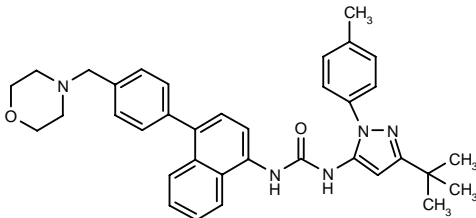
SOURCE – Boehringer Ingelheim.

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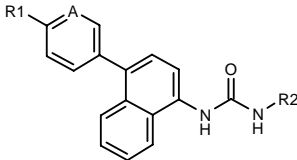
295076

N-[3-*tert*-Butyl-1-(4-methylphenyl)-1 *H*-pyrazol-5-yl]-*N'*-[4-[4-(4-morpholinylmethyl)phenyl]naphthalen-1-yl]urea



C36 H39 N5 O2; Mol wt: 573.7371

ACTION – An inhibitor of the release of inflammatory cytokines such as IL-1 and TNF, with potential for the treatment of inflammatory and autoimmune disorders, osteoporosis, Alzheimer’s disease, acute and chronic pain, stroke, myocardial infarction, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses, hemodialysis and enterocolitis. Other specifically claimed aromatic heterocyclic compounds include the following:



Compound	R1	R2	A	Formula
295078	3-OH-1-Pip-CH2	3-t-Bu-1-(6-Me-3-Pyr)-5-pyrazolyl	CH	C ₃₆ H ₄₀ N ₆ O ₂
295079	tetrahydro-4-thiopyranyl-NH	3-t-Bu-1-(6-Me-3-Pyr)-5-pyrazolyl	N	C ₃₄ H ₃₇ N ₇ OS
295080	4-morpholinyl-CH2	3-t-Bu-1-[3-[MeS(CH2)3]-4-pyrazolyl]-5-pyrazolyl	N	C ₃₅ H ₄₂ N ₈ O ₂ S
295081	4-morpholinyl-CH2	5-t-Bu-2-Ph-Ph	N	C ₃₇ H ₃₈ N ₄ O ₂
295083	4-morpholinyl-CH2	3-(AcNH)-5-t-Bu-2-MeO-Ph	N	C ₃₄ H ₃₉ N ₅ O ₄
295084	4-morpholinyl-CH2	5-t-Bu-2-PrO-Ph	N	C ₃₄ H ₄₀ N ₄ O ₃
295085	4-morpholinyl-CH2	5-CF3-2-MeSO-Ph	N	C ₂₉ H ₂₇ F ₃ N ₄ O ₃ S
295086	4-morpholinyl-CH2	5-t-Bu-2-MeS-Ph	N	C ₃₂ H ₃₆ N ₄ O ₂ S
295087	3-oxo-1-Piz-CH2	5-t-Bu-2-MeO-Ph	N	C ₃₂ H ₃₅ N ₅ O ₃

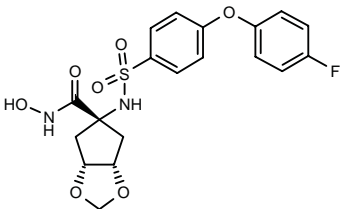
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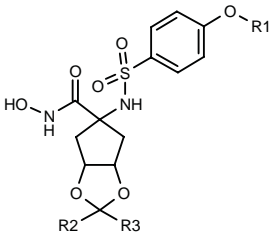
295131

[3a*R*-(3α,5β,6α)]-5-[4-(4-Fluorophenoxy)phenylsulfon-amido]tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole-5-carboxydroxamic acid



C19 H19 F N2 O7 S; Mol wt: 438.4301

ACTION – Selective inhibitor of the matrix metallo-proteinase MMP-13 (collagenase 3), potentially useful for the treatment of a variety of diseases including arthritis and cancer. Other specifically claimed dioxocyclopentyl hydroxamides are:



Compound	R1	R2	R3	Isomer	Formula
295132	4-F-Ph	H	H	3a <i>S</i> -(3α,5α,6α)	C ₁₉ H ₁₉ FN ₂ O ₇ S
295133	4-Cl-Ph	H	H	3a <i>R</i> -(3αβ,5α,6αβ)	C ₁₉ H ₁₉ ClN ₂ O ₇ S
295134	4-Cl-Ph	H	H	3a <i>S</i> -(3α,5α,6α)	C ₁₉ H ₁₉ ClN ₂ O ₇ S
295135	4-F-Ph	-O-		3a <i>R</i> -(3αβ,5α,6αβ)	C ₁₉ H ₁₇ FN ₂ O ₈ S
295136	CH2Ph	H	H	3a <i>S</i> -(3α,5α,6α)	C ₂₀ H ₂₂ N ₂ O ₇ S
295137	4-F-PhCH2	H	H	3a <i>S</i> -(3α,5α,6α)	C ₂₀ H ₂₁ FN ₂ O ₇ S

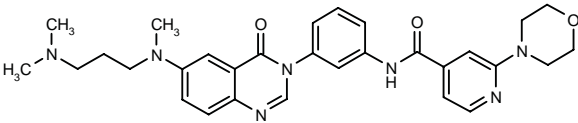
SOURCE – Pfizer.

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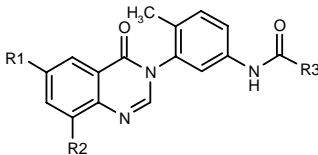
295142

N-[3-[6-[*N*-[3-(Dimethylamino)propyl]-*N*-methylamino]-3,4-dihydro-4-oxoquinazolin-3-yl]phenyl]-2-(4-morpholinyl)pyridine-4-carboxamide



C30 H35 N7 O3; Mol wt: 541.6525

ACTION – An inhibitor of the production of cytokines such as TNF-α and various interleukins such as IL-1, IL-6 and IL-8, with potential in the treatment of cytokine-mediated disorders such as rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischemic heart disease and psoriasis. Compound was shown to inhibit p38α kinase activity with an IC₅₀ of about 0.05 μM and lipopolysaccharide-stimulated TNF-α production in human whole blood with an IC₅₀ of approximately 5 μM. Other specifically claimed compounds from this series of amide derivatives include the following:



Compound	R1	R2	R3	Formula
295143	N(Me)(CH2)3-N(Me)2	H	2-(4-morpholinyl)-4-Pyr	C ₃₁ H ₃₇ N ₇ O ₃
295144	H	N(Me)(CH2)3-N(Me)2	2-(4-morpholinyl)-4-Pyr	C ₃₁ H ₃₇ N ₇ O ₃
295145	4-Me-1-Piz	H	2-(1-Pip)-4-Pyr	C ₃₁ H ₃₆ N ₇ O ₂
295146	4-Me-1-Piz	H	dibenzofuran-4-yl	C ₃₃ H ₂₉ N ₅ O ₃
295147	4-Me-1-Piz	H	3-AcNH-Ph	C ₂₉ H ₃₀ N ₆ O ₃

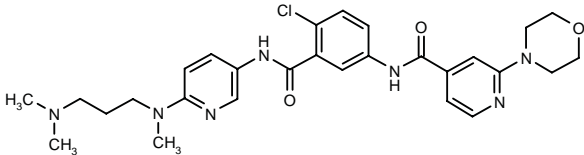
SOURCE – AstraZeneca.

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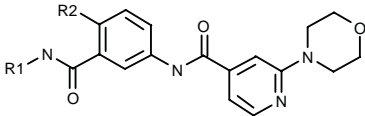
295148

N-[4-Chloro-3-[*N*-[6-[*N*-[3-(dimethylamino)propyl]-*N*-methylamino]pyridin-3-yl]carbamoyl]phenyl]-2-(4-morpholinyl)pyridine-4-carboxamide



C28 H34 Cl N7 O3; Mol wt: 552.0756

ACTION – An inhibitor of the production of cytokines such as TNF- α and various interleukins such as IL-1, IL-6 and IL-8, with potential in the treatment of cytokine-mediated disorders such as rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischemic heart disease and psoriasis. Compound was shown to inhibit p38 α kinase activity with an IC₅₀ of about 0.05 μ M and lipopolysaccharide-stimulated TNF- α production in human whole blood with an IC₅₀ of approximately 5 μ M. Other specifically claimed compounds from this series of amide derivatives include the following:



Compound	R1	R2	Formula
295149	6-(4-Et-1-Piz)-3-Pyr	Cl	C ₂₈ H ₃₂ ClN ₇ O ₃
295150	6-(4-Me-1-Piz)-3-Pyr	Cl	C ₂₇ H ₃₀ ClN ₇ O ₃
295151	3-(4-Me-1-Piz-CH2)-Ph	Me	C ₃₀ H ₃₆ N ₆ O ₃

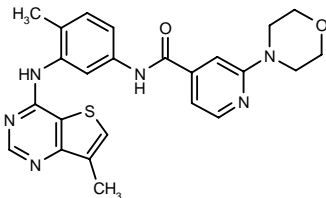
SOURCE – AstraZeneca.

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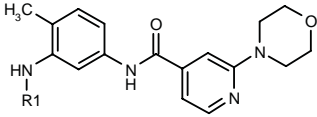
295258

N-[4-Methyl-3-(7-methylthieno[3,2-*d*]pyrimidin-4-ylamino)phenyl]-2-(4-morpholinyl)pyridine-4-carboxamide



C24 H24 N6 O2 S; Mol wt: 460.5596

ACTION – Agent for the treatment of cytokine-mediated disorders that acts via inhibition of p38 kinase (IC₅₀ = 0.04 μ M for inhibition of p38 α). The compound is reported to inhibit lipopolysaccharide-stimulated TNF- α production and to demonstrate antiarthritic activity in a collagen-induced arthritis model in mice. Other exemplified compounds from this series of pyridine and pyrimidine derivatives are:



Compound	R1	Formula
295259	thieno[3,2-d]pyrimidin-4-yl	C ₂₃ H ₂₂ N ₆ O ₂ S
295261	5-Me-thieno[2,3-d]pyrimidin-4-yl	C ₂₄ H ₂₄ N ₆ O ₂ S
295262	thieno[2,3-d]pyrimidin-4-yl	C ₂₃ H ₂₂ N ₆ O ₂ S

SOURCE – AstraZeneca.

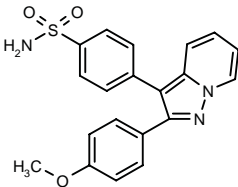
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FR-228352

296946

4-[2-(4-Methoxyphenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-benzenesulfonamide



C20 H17 N3 O3 S; Mol wt: 379.4383

ACTION – Antiinflammatory agent, an inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.12 and 0.075 mM in recombinant and whole blood assays, respectively) with more than 70-fold selectivity over COX-1 (IC₅₀ = 8.1 and 6.1 mM in recombinant and whole blood assays, respectively) and 10-fold greater potency than indomethacin in the recombinant assay. Compound exhibited potent antiarthritic and analgesic activity in the rat adjuvant arthritic model, giving 63 and 69% inhibition of swelling, respectively, compared to the untreated paw at doses of 1.0 and 3.2 mg/kg p.o., as well as an increase in pain threshold in the inflamed paw.

SOURCE – Fujisawa.

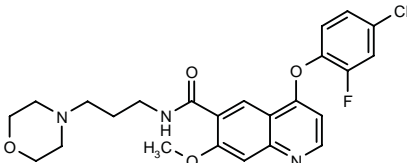
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IMMUNOMODULATING AGENTS

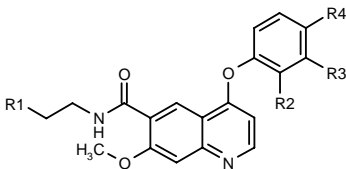
294124

4-(4-Chloro-2-fluorophenoxy)-7-methoxy-N-[3-(4-morpholinyl)propyl]quinoline-6-carboxamide



C24 H25 Cl F N3 O4; Mol wt: 473.9295

ACTION – Nonreceptor tyrosine kinase inhibitor with potent activity against p56^{lck} tyrosine kinase, while demonstrating reduced or no significant activity against other nonreceptor tyrosine kinases or receptor tyrosine kinases such as epidermal growth factor (EGF) or vascular endothelial growth factor (VEGF) receptor kinases. This compound inhibited the p56^{lck}-induced phosphorylation of a tyrosine-containing polypeptide substrate (IC₅₀ about 0.03 μM) and T-cell proliferation in human peripheral blood mononuclear cells (IC₅₀ about 18 μM). It is thus useful as an immunomodulator or immunosuppressant in the treatment of transplant rejection and rheumatoid arthritis. Other specifically claimed quinoline derivatives are:



Compound	R1	R2	R3	R4	Formula
294126	4-morpholinyl-CH2	H	Cl	Cl	C ₂₄ H ₂₅ Cl ₂ N ₃ O ₄
294128	2-oxo-1-imidazolidinyl	F	H	Cl	C ₂₂ H ₂₀ ClFN ₄ O ₄
294129	4-morpholinyl-CH2	H	H	OPh	C ₃₀ H ₃₁ N ₃ O ₅

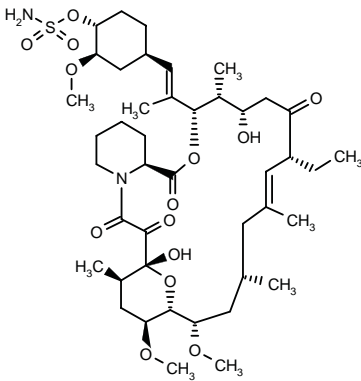
SOURCE – AstraZeneca.

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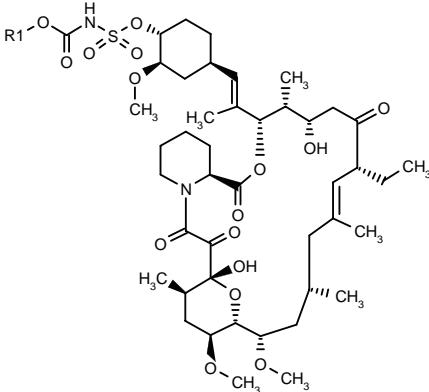
294302

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*R*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-17-Ethyl-1,14-dihydroxy-23,25-dimethoxy-12-[2-[3-methoxy-4-(sulfamoyloxy)cyclohexyl]-1(*E*)-methylvinyl]-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone



C43 H70 N2 O14 S; Mol wt: 871.0920

ACTION – Semisynthetic macrolide with immunosuppressant activity and reduced side effects. Immunosuppressant activity was demonstrated in the human mixed lymphocyte reaction (MLR) assay (IC₅₀ = 0.82 nM). It was also tested *in vivo* in a whole blood concentration assay in rats, where it showed complete elimination from blood 2 h after p.o., i.p. and i.v. doses of 5 mg/kg. Other exemplified macrolides are:



Compound	R1	Formula
294303	Me	C ₄₅ H ₇₂ N ₂ O ₁₆ S
294304	Et	C ₄₆ H ₇₄ N ₂ O ₁₆ S
294305	CH2Ph	C ₅₁ H ₇₆ N ₂ O ₁₆ S
294306	t-Bu	C ₄₈ H ₇₈ N ₂ O ₁₆ S
294307	cyclohexyl	C ₅₀ H ₈₀ N ₂ O ₁₆ S
294308	cycloheptyl	C ₅₁ H ₈₂ N ₂ O ₁₆ S
294309	4-Pyr-CH2	C ₅₀ H ₇₅ N ₃ O ₁₆ S
294310	3-Pyr-CH2	C ₅₀ H ₇₅ N ₃ O ₁₆ S
294311	2-Pyr-CH2	C ₅₀ H ₇₅ N ₃ O ₁₆ S
294312	4-NO2-PhCH2	C ₅₁ H ₇₅ N ₃ O ₁₈ S

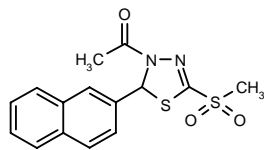
SOURCE – Abbott.

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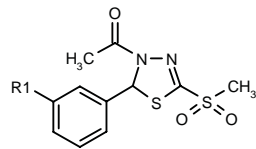
294806

1-[5-(Methylsulfonyl)-2-(2-naphthyl)-2,3-dihydro-1,3,4-thiadiazol-3-yl]ethan-1-one



C15 H14 N2 O3 S2; Mol wt: 334.4186

ACTION – Immunomodulator, a STAT6 activation inhibitor, potentially useful in the treatment or prophylaxis of allergic disorders, parasitic infections, autoimmune diseases, viral or bacterial infections, cancer, graft-versus-host disease and AIDS. Other exemplified thiadiazoles include the following:



Compound	R1	Formula
294807	H	C ₁₁ H ₁₂ N ₂ O ₃ S ₂
294808	OMe	C ₁₂ H ₁₄ N ₂ O ₄ S ₂
294809	Cl	C ₁₁ H ₁₁ ClN ₂ O ₃ S ₂

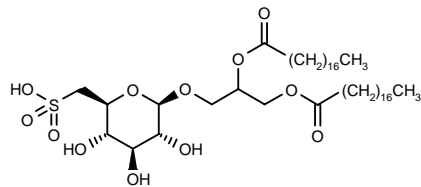
SOURCES – Sumitomo Chemical; Sumitomo Pharmaceuticals.

REFERENCES

1. Inoue, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.; Sumitomo Chemical Co., Ltd.) *STAT6 activation inhibitors*. JP 2000229959.

294814

3-O-(6-Deoxy-6-sulfo-β-D-glucopyranosyl)-1,2-di-O-octadecanoyl-sn-glycerol



C45 H86 O12 S; Mol wt: 851.2284

ACTION – Immunosuppressant active in the human mixed lymphocyte reaction (MLR) assay and able to decrease epidermal necrosis in a model of skin transplant rejection in rats.

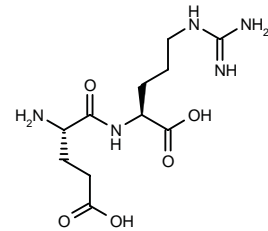
SOURCE – Toyo Suisan.

REFERENCES

1. Yamazaki, T. et al. (Toyo Suisan Co., Ltd.) *Novel immunosuppressants*. WO 0053190.

294845

L-Glutamyl-L-arginine



C11 H21 N5 O5; Mol wt: 303.3169

ACTION – Antiinflammatory and immunomodulating agent that acts by inhibiting macrophage migration and/or macrophage phagocytic activity; in addition, compound also inhibits the ability of macrophages and T-cells to adhere to extracellular matrix and/or fibronectin and upregulate Fas receptor expression in T-cells, and it further exhibits an inhibitory effect on humoral and/or cellular immune responses. *In vitro*, compound inhibited human T-cell adhesion to retinal extracellular matrix. In *in vivo* experiments, it was shown to delay the time of onset and reduce the severity of experimental allergic encephalitis induced by myelin immunization in rats when given at 15 µg/day i.p., as well as to reduce the severity of lipopoly-saccharide-induced uveitis in rabbit eyes when given at 200 µg intraocularly, as measured by a decrease in the number of invading lymphocytes.

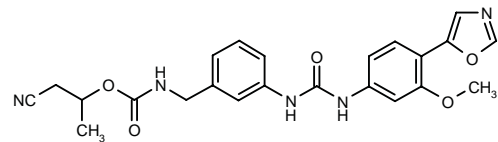
SOURCE – Yeda.

REFERENCES

1. Eisenbach-Schwartz, M. et al. (Yeda Research & Development Co. Ltd.) *Anti-inflammatory dipeptide and pharmaceutical compsn. thereof*. JP 2001500491, JP 2001500492, US 6126939, WO 9809984, WO 9809985.

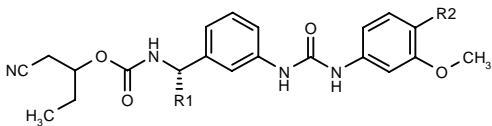
295175

N-[3-[3-[3-Methoxy-4-(5-oxazolyl)phenyl]ureido]-benzyl]carbamic acid 2-cyano-1-methylethyl ester



C23 H23 N5 O5; Mol wt: 449.4647

ACTION – IMP dehydrogenase (IMPDH) inhibitor (K_i = 10 nM or less), potentially useful for the treatment of transplant rejection, graft-versus-host disease, autoimmune and inflammatory diseases, for inhibiting viral replication and vascular cellular hyperproliferation, and for the treatment of cancer, particularly lymphoma and leukemia. Other exemplified compounds include the following:



Compound	R1	R2	Isomer	Formula
295177	H	5-oxazolyl		C ₂₄ H ₂₈ N ₅ O ₅
295178	Me	CN	R	C ₂₃ H ₂₈ N ₅ O ₄
295179	Me	5-oxazolyl	R	C ₂₅ H ₂₇ N ₅ O ₅

SOURCE – Vertex.

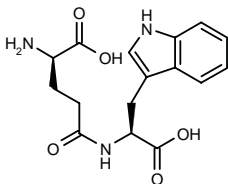
REFERENCES

1. Stamos, D. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of IMPDH enzyme*. WO 0056331.

SCV-07

280440

γ-D-Glutamyl-L-tryptophan



C16 H19 N3 O5; Mol wt: 333.3421

ACTION – Immunomodulating agent, a synthetic dipeptide proven to stimulate T-lymphocyte differentiation and IL-2 production in murine bone marrow T-cell precursors and human peripheral blood lymphocytes, respectively. In mice, compound was found to stimulate a specific immune response to ovalbumin, increasing total anti-ovalbumin IgG titers in serum after both primary and secondary immunization, and to stimulate IL-2 and interferon gamma production in the spleen after secondary immunization, without affecting IL-4 production. Potentially useful for selectively switching to a Th1 response in allergic patients.

SOURCES – University of California, Berkeley, Berkeley, CA (US); SciClone.

REFERENCES

1. Wei, E.T. et al. *γ-Glutamyl and β-aspartyl containing immunomodulator cpds. and methods therewith*. WO 9933799.

2. Simbirtsev, A. et al. *Immunomodulatory activity of a novel synthetic peptide γ-D-glutamyl-L-tryptophan*. 17th Int Congr Allergol Clin Immunol (Oct 15-20, Sidney) 2000, Abst P-787.

3. *SciClone awarded grant to study novel immunomodulator in TB*. DailyDrugNews.com (Daily Essentials) 2000, Feb 25.

4. *SciClone licenses new class of immunomodulators from University of California*. DailyDrugNews.com (Daily Essentials) 1999, Aug 31.

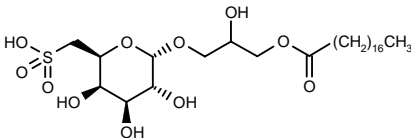
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

294414

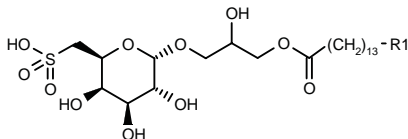
3-*O*-(6-Deoxy-6-sulfo-α-D-galactopyranosyl)-1-*O*-octadecanoyl-*sn*-glycerol

6-Deoxy-1-*O*-[2-hydroxy-3-(octadecanoyloxy)propyl]-α-D-galactopyranos-6-ylsulfonic acid



C27 H52 O11 S; Mol wt: 584.7628

ACTION – Antineoplastic agent, a DNA synthase inhibitor (IC₅₀ = 5.0 μg/ml) proven active *in vitro* against colon cancer DLD-1 and gastric cancer NUGC-3 cells (IC₅₀ = 27.5 and 30.3 μg/ml, respectively). Other exemplified sulfofucosylacylglycerol derivatives are:



Compound	R1	Formula
294415	H	C ₂₃ H ₄₄ O ₁₁ S
294416	Et	C ₂₅ H ₄₈ O ₁₁ S

SOURCE – Toyo Suisan.

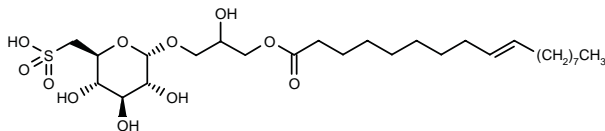
REFERENCES

1. Yamazaki, T. et al. (Toyo Suisan Co., Ltd.) *Novel sulfofucosylacylglycerol derivs. and utilization thereof as drugs*. WO 0052021.

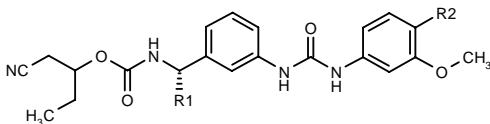
294419

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-(9-octadecenoyl)-*sn*-glycerol

6-Deoxy-1-*O*-[2-hydroxy-3-(9-octadecenoyloxy)propyl]-α-D-glucopyranos-6-ylsulfonic acid



C27 H50 O11 S; Mol wt: 582.7470



Compound	R1	R2	Isomer	Formula
295177	H	5-oxazolyl		C ₂₄ H ₂₈ N ₅ O ₅
295178	Me	CN	R	C ₂₃ H ₂₈ N ₅ O ₄
295179	Me	5-oxazolyl	R	C ₂₅ H ₂₇ N ₅ O ₅

SOURCE – Vertex.

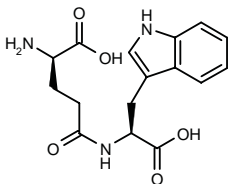
REFERENCES

1. Stamos, D. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of IMPDH enzyme*. WO 0056331.

SCV-07

280440

γ-D-Glutamyl-L-tryptophan



C16 H19 N3 O5; Mol wt: 333.3421

ACTION – Immunomodulating agent, a synthetic dipeptide proven to stimulate T-lymphocyte differentiation and IL-2 production in murine bone marrow T-cell precursors and human peripheral blood lymphocytes, respectively. In mice, compound was found to stimulate a specific immune response to ovalbumin, increasing total anti-ovalbumin IgG titers in serum after both primary and secondary immunization, and to stimulate IL-2 and interferon gamma production in the spleen after secondary immunization, without affecting IL-4 production. Potentially useful for selectively switching to a Th1 response in allergic patients.

SOURCES – University of California, Berkeley, Berkeley, CA (US); SciClone.

REFERENCES

1. Wei, E.T. et al. *γ-Glutamyl and β-aspartyl containing immunomodulator cpds. and methods therewith*. WO 9933799.

2. Simbirtsev, A. et al. *Immunomodulatory activity of a novel synthetic peptide γ-D-glutamyl-L-tryptophan*. 17th Int Congr Allergol Clin Immunol (Oct 15-20, Sidney) 2000, Abst P-787.

3. *SciClone awarded grant to study novel immunomodulator in TB*. DailyDrugNews.com (Daily Essentials) 2000, Feb 25.

4. *SciClone licenses new class of immunomodulators from University of California*. DailyDrugNews.com (Daily Essentials) 1999, Aug 31.

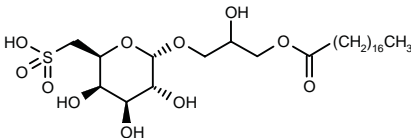
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

294414

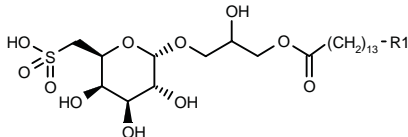
3-*O*-(6-Deoxy-6-sulfo-α-D-galactopyranosyl)-1-*O*-octadecanoyl-*sn*-glycerol

6-Deoxy-1-*O*-[2-hydroxy-3-(octadecanoyloxy)propyl]-α-D-galactopyranos-6-ylsulfonic acid



C27 H52 O11 S; Mol wt: 584.7628

ACTION – Antineoplastic agent, a DNA synthase inhibitor (IC₅₀ = 5.0 μg/ml) proven active *in vitro* against colon cancer DLD-1 and gastric cancer NUGC-3 cells (IC₅₀ = 27.5 and 30.3 μg/ml, respectively). Other exemplified sulfofucosylacylglycerol derivatives are:



Compound	R1	Formula
294415	H	C ₂₃ H ₄₄ O ₁₁ S
294416	Et	C ₂₅ H ₄₈ O ₁₁ S

SOURCE – Toyo Suisan.

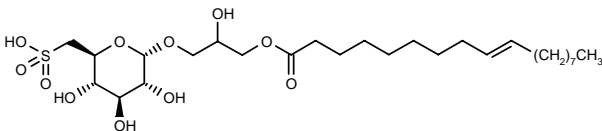
REFERENCES

1. Yamazaki, T. et al. (Toyo Suisan Co., Ltd.) *Novel sulfofucosylacylglycerol derivs. and utilization thereof as drugs*. WO 0052021.

294419

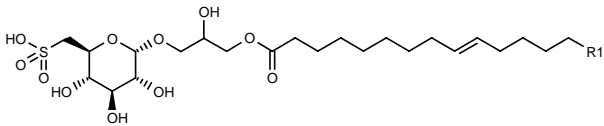
3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-(9-octadecenoyl)-*sn*-glycerol

6-Deoxy-1-*O*-[2-hydroxy-3-(9-octadecenoyloxy)propyl]-α-D-glucopyranos-6-ylsulfonic acid



C27 H50 O11 S; Mol wt: 582.7470

ACTION – Antineoplastic agent, a DNA synthase inhibitor (IC₅₀ = 2.0 µg/ml) proven active *in vivo* in increasing tumor growth delay of s.c.-implanted human lung carcinoma A549 in mice. Other exemplified sulfopyranosylacylglycerol derivatives are:



Compound	R1	Formula
294422	H	C ₂₃ H ₄₂ O ₁₁ S
294424	Et	C ₂₅ H ₄₆ O ₁₁ S

SOURCE – Toyo Suisan.

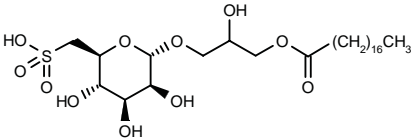
REFERENCES

1. Yamazaki, T. et al. (Toyo Suisan Co., Ltd.) *Drugs containing sulfoquinosylacylglycerol derivs.* WO 0051622.

2. Hanashima, S. et al. *Synthesis of sulfoquinosylacylglycerols, inhibitors of eukaryotic DNA polymerase α and β.* Bioorg Med Chem 2001, 9(2): 367.

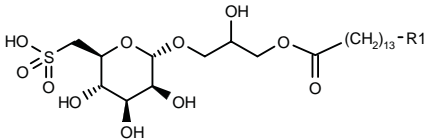
294803

(±)-1-*O*-(6-Deoxy-6-sulfo-α-D-mannopyranosyl)-3-*O*-octadecanoyl-*sn*-glycerol



C27 H52 O11 S; Mol wt: 584.7628

ACTION – Antineoplastic agent, a DNA synthase inhibitor (IC₅₀ = 2.0 and 6.71 µg/ml for inhibition of DNA synthase α and β, respectively) active *in vitro* against colon cancer DLD-1 (IC₅₀ = 14 µg/ml) and gastric cancer NUGC-3 cells (IC₅₀ = 28.5 µg/ml). Other exemplified sulforhamnosylacylglycerol derivatives are:



Compound	R1	Formula
294804	H	C ₂₃ H ₄₄ O ₁₁ S
294805	Et	C ₂₅ H ₄₈ O ₁₁ S

SOURCE – Toyo Suisan.

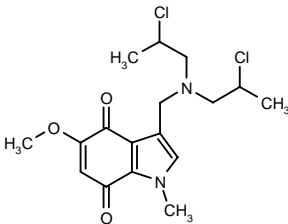
REFERENCES

1. Yamazaki, T. et al. (Toyo Suisan Co., Ltd.) *Novel sulforhamnosylacylglycerol derivs. and utilization thereof as drugs.* WO 0052020.

MUP-98176

295988

3-[Bis(2-chloropropyl)aminomethyl]-5-methoxy-1-methyl-1*H*-indole-4,7-dione



C17 H22 Cl2 N2 O3; Mol wt: 373.2778

ACTION – Antineoplastic agent, an indolequinone–mustard conjugate that releases the mustard preferentially under hypoxic (reductive) conditions. Whereas the mustard was similarly potent under both aerobic and hypoxic conditions (IC₅₀ = 0.17 and 0.11 µM, respectively), the prodrug was much more toxic under hypoxic than under aerobic conditions (IC₅₀ = 0.07 and 34 µM, respectively).

SOURCE – University of Manchester, Manchester (GB).

REFERENCES

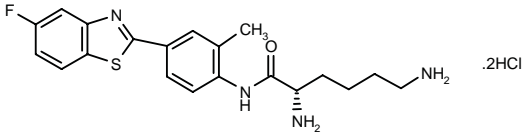
1. Jaffar, M. et al. *Novel indolequinone-mustard conjugates with enhanced hypoxic selectivity.* Clin Cancer Res 2000, 6(Suppl.): Abst 308.

NSC-710305

295753

*N*¹-[4-(5-Fluorobenzothiazol-2-yl)-2-methylphenyl]-L-lysine dihydrochloride

5F-DF-203-L-lysine dihydrochloride



C20 H23 F N4 O S . 2HCl; Mol wt: 459.4145

ACTION – Water-soluble prodrug of the highly cytotoxic compound NSC-703786*, thought to act by inducing cytochrome P-450 CYP1A1 and/or CYP1B1, followed by the induction of DNA damage in sensitive cells. *In vivo*, the prodrug released the free base at plasma concentrations exceeding those required for cytotoxic activity for over 6 h following a single i.v. infusion. The prodrug is expected to enter clinical trials this year.

SOURCE – University of Nottingham, Nottingham (GB).

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1. Bradshaw, T.D. et al. *Preclinical evaluation of fluorinated 2-(4-aminophenyl)-benzothiazoles*. Clin Cancer Res 2000, 6(Suppl.): Abst 475.
2. Hutchinson, I. et al. *Synthesis of fluorinated 2-(4-aminophenyl)benzothiazoles and their prodrugs*. Clin Cancer Res 2000, 6(Suppl.): Abst 152.

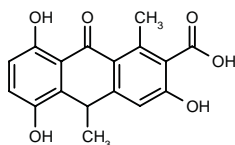
*See **5F-203** Drug Data Rep 2000, 022(08): 0749.

ANTIBIOTICS AND ALKALOIDS

CHT-22

294657

3,5,8-Trihydroxy-1,10-dimethyl-9-oxo-9,10-dihydroanthracene-2-carboxylic acid



C17 H14 O6; Mol wt: 314.2916

ACTION – Antineoplastic antibiotic isolated from *Streptomyces* sp. 576H-11 (FERM BP-6573), found to inhibit the proliferation of human cervical cancer HeLaS3 and renal cancer ACHN cells with respective IC₅₀ values of 287 and 474 μ M.

SOURCE – Kyowa Hakko.

REFERENCES

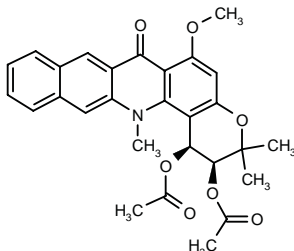
1. Ogawa, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *CHT22 cpds*. JP 2000229908.

S-23906-1*

278584

(+)-*cis*-1,2-Bis(acetox)-6-methoxy-3,3,14-trimethyl-2,3,7,14-tetrahydro-1*H*-benzo[b]pyrano[3,2-*h*]acridin-7-one

S-23906



C28 H27 N O7; Mol wt: 489.5213

ACTION – Antineoplastic agent, a potent synthetic derivative of acronycine with strong cytotoxic activity against murine and human tumor cells *in vitro* (IC₅₀ = 0.035-0.8 μ M). At cytotoxic concentrations, compound induced irreversible accumulation of cells in the S phase followed by apoptosis, whereas lower concentrations resulted in accumulation of cells in the G2/M phase of the cell cycle. Preliminary experiments showed that compound interacts with purified supercoiled DNA without inhibiting topoisomerases I or II. *In vivo*, it was apparently selective for human solid tumors, showing antitumor activity comparable to paclitaxel, vinorelbine and irinotecan against ovarian, lung and colon carcinoma xenografts in nude mice after both i.v. and p.o. administration. Selected for further preclinical investigation.

SOURCE – Servier.

REFERENCES

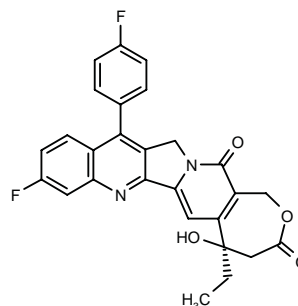
1. Koch, M. et al. (ADIR et Cie.) *Novel acronycine derivs., preparation method and pharmaceutical compsns*. EP 1042326, FR 2772765, WO 9932491.
2. Costes, N. et al. *Synthesis and cytotoxic and antitumor activity of benzo[b]pyrano[3,2-*h*]acridin-7-one analogues of acronycine*. J Med Chem 2000, 43(12): 2395.
3. Nicolas, G. et al. *Preclinical antitumor activity of S 23906-1, a new acronycine derivative, in human orthotopic models*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3819.
4. Pierré, A. et al. *Antitumor activity of new potent acronycine derivatives*. Clin Cancer Res 2000, 6(Suppl.): Abst 476.
5. Stephane, L. et al. *Cytotoxicity and cell cycle effect of S23906-1, a new acronycine derivative*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3827.

*Identified compound **278584** (see **278583**) Drug Data Rep 1999, 021(09): 0820.

DNA-INTERCALATING DRUGS

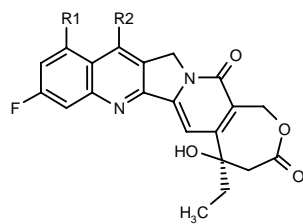
294096

5(*R*)-Ethyl-9-fluoro-12-(4-fluorophenyl)-5-hydroxy-1,3,4,5,13,15-hexahydrooxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione



C27 H20 F2 N2 O4; Mol wt: 474.4610

ACTION – An inhibitor of topoisomerase I and/or II with potential as an anticancer, antiviral and antiparasitic agent. *In vitro*, compound exhibited an IC₅₀ value of 0.26 nM against human colon adenocarcinoma HT-29 cells. Other exemplified compounds from this series of optically active β -hydroxylactone analogues of camptothecin include the following:



Compound	R1	R2	Formula
294097	H	3,5-(F)2-Ph	C ₂₇ H ₁₉ F ₃ N ₂ O ₄
294098	H	4-CF3-Ph	C ₂₈ H ₂₀ F ₄ N ₂ O ₄
294099	F	CH2CH2OEt	C ₂₅ H ₂₄ F ₂ N ₂ O ₅

SOURCE – SCRAS.

REFERENCES

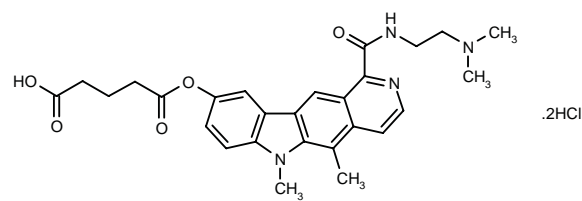
1. Lavergne, O. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Optically pure camptothecin analogues*. FR 2790261, WO 0050427.

S-30972-1*

268354

9-(4-Carboxybutyryloxy)-N-[2-(dimethylamino)ethyl]-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide dihydrochloride

Pentanedioic acid [1-[N-[2-(dimethylamino)ethyl]carbamoyl]-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-yl] mono-ester dihydrochloride



C27 H30 N4 O5 . 2HCl; Mol wt: 563.4788

ACTION – Antineoplastic agent, a topoisomerase II inhibitor derived from olivacine with strong cytotoxic activity against human tumor cell lines including glioblastomas U-373 and U-87, non-small cell lung cancer A549 and A-427, and colon cancer HCT-15 and LoVo cells (IC₅₀ = 310, 110, 337, 72, 79 and 42 nM, respectively). Compound arrested the cell cycle in the G2 phase and induced ATP-dependent topoisomerase II inhibition and apoptosis in highly proliferating human glioblastoma U-373 cells. It also exhibited antitumor activity in mice bearing leukemia P388 or L1210, lymphoma P388 or L1210, hormone-sensitive and -insensitive variants of mammary carcinoma MXT and B16 melanoma, giving respective T/C values of > 300%, > 300%, 136%, 163%, 153%, > 300% and 184% at a dose of 20 mg/kg i.p. In these models, compound showed comparable activity to etoposide and was generally more effective than doxorubicin.

SOURCE – Servier.

REFERENCES

1. Guillonnet, C. et al. (ADIR et Cie.) *Ellipticine derivs., their preparation and pharmaceutical compns. containing them*. EP 0850940, US 6162811.

2. Guillonnet, C. et al. *Synthesis of 9-O-substituted derivatives of 9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (2-(dimethylamino)ethyl)amide and their 10- and 11-methyl analogues with improved antitumor activity*. J Med Chem 1999, 42(12): 2191.

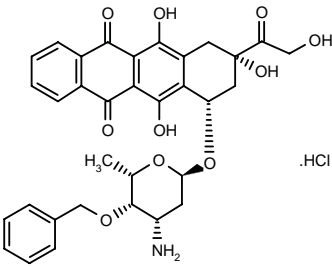
3. Malonne, H. et al. *In vitro and in vivo pharmacological characterizations of the antitumor properties of two new olivacine derivatives, S16020-2 and S30972-1*. Clin Cancer Res 2000, 6(9): 3774.

*Identified compound **268354** (see **268352**) Drug Data Rep 1998, 020(11): 0989.

WP-769

287326

7-O-(4-O-Benzyl-2,6-dideoxy-α-L-galactopyranosyl)-4-demethoxyadriamycinone hydrochloride



C33 H33 N O10 . HCl; Mol wt: 640.0816

ACTION – Antineoplastic agent, an orally active, mechanistically altered doxorubicin analogue with improved activity against multidrug-resistant tumor cells and strong *in vivo* activity after oral administration. Compound was found to induce apoptosis and topoisomerase II-mediated DNA–protein crosslinks in CEM cells. WP-769 was designed based on the hypothesis that an increased ability to circumvent multidrug resistance mechanisms would reduce first-pass cytochrome P-450-mediated drug metabolism and thereby increase oral bioavailability.

SOURCE – M.D. Anderson Cancer Center, Houston, TX (US).

REFERENCES

1. Priebe, W. et al. *Methods and compns. for the manufacture of C-3' and C-4' anthacycline antibiotics*. WO 0056267.

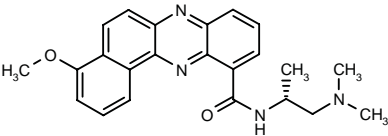
2. Priebe, I. et al. *WP769, a novel orally active mechanistically altered doxorubicin analog*. Clin Cancer Res 2000, 6(Suppl.): Abst 358.

3. Priebe, W. *WP769, a novel orally active doxorubicin analog*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1810.

XR-11576

287947

N-[2-(Dimethylamino)-1(R)-methylethyl]-4-methoxybenzo-[a]phenazine-11-carboxamide



C23 H24 N4 O2; Mol wt: 388.4686

ACTION – Antineoplastic agent, a dual topoisomerase I and II inhibitor with strong cytotoxic activity against a panel of human and murine cancer cell lines including cell lines derived from solid tumors (colon, ovarian and lung), as well as of leukemic origin ($IC_{50} = 10\text{-}50\text{ nM}$). Similar potency was maintained against cell lines displaying atypical drug resistance due to downregulation of topoisomerase II. In pharmacokinetic studies in nude mice bearing solid tumors, compound at a dose of 20 mg/kg i.v. showed a plasma half-life of 3.2 h and a large volume of distribution, with consequently relatively high levels in tumor tissue; the oral bioavailability in mice was 72%. Compound exhibited significant antitumor activity in nude mice bearing refractory human colon adenocarcinoma HT-29 (T/C = 28%) after both i.v. (52.5 mg/kg) and oral (75 mg/kg) doses given every 7 days for 3 doses. It was also effective in inducing tumor growth delay in animals bearing small cell lung carcinoma H69/P on this same schedule at i.v. doses of 30 and 45 mg/kg and oral doses of 50 and 65 mg/kg. In both tumor models, its efficacy was comparable to that of equimolar doses of TAS-103 and the compound was well tolerated at effective doses. Selected as a candidate for further development.

SOURCE – Xenova.

REFERENCES

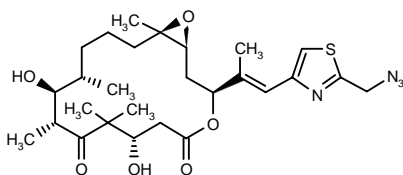
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3. *Xenova highlights 1999 clinical progress*. DailyDrugNews.com (Daily Essentials) 2000, April 4.
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ANTIMITOTIC DRUGS

294110

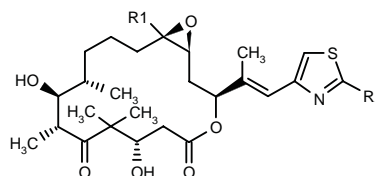
[1*R**,3*R**(*E*),7*R**,10*S**,11*R**,12*R**,16*S**]-3-[2-[2-(Azidomethyl)thiazol-4-yl]-1-methylvinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

[4*R**,7*S**,8*R**,9*R**,13*S**,14*R**,16*R**(*E*)]-16-[2(*E*)-[2-(Azidomethyl)thiazol-4-yl]-1-methylvinyl]-13,14-epoxy-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxacyclohexadecane-2,6-dione



C₂₇ H₄₀ N₄ O₆ S; Mol wt: 548.7010

ACTION – Agent for the treatment of cancer and other hyperproliferative disorders that acts by stabilizing microtubules. Compound is also reported to inhibit angiogenesis and modulate apoptosis, and may thus be further used for the treatment of blindness related to retinal vascularization, arthritis, multiple sclerosis, restenosis, kidney diseases and viral infections. *In vitro*, compound exhibited cytotoxic activity against murine fibroblast L929, human cervical carcinoma KB-3.1 and multidrug-resistant KB-V1 and human prostate adenocarcinoma PC-3 cells ($IC_{50} = 0.6, 0.5, 0.5$ and 0.4 ng/ml , respectively). Other exemplified compounds from this series of C-21 modified epothilones include the following:



Compound	R1	R2	Formula
294117	H	CH ₂ Cl	C ₂₆ H ₃₈ ClNO ₆ S
294118	H	CH ₂ NH ₂	C ₂₆ H ₄₀ N ₂ O ₆ S
294120	H	vinyl	C ₂₇ H ₃₉ NO ₆ S
294121	Me	CH ₂ NH ₂	C ₂₇ H ₄₂ N ₂ O ₆ S

SOURCES – Bristol-Myers Squibb; GBF.

REFERENCES

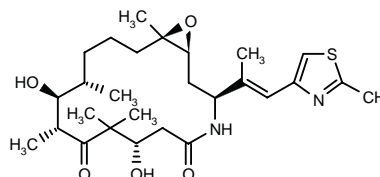
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BMS-247550

293356

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione

16-Aza-epothilone B



C₂₇ H₄₂ N₂ O₅ S; Mol wt: 506.7038

ACTION – Antineoplastic agent, a semisynthetic epothilone B analogue that induces tubulin polymerization. Preclinical testing showed tubulin activity and cytotoxicity comparable to paclitaxel ($EC_{0.01} = 3.8\text{ }\mu\text{M}$; IC_{50} against human colon carcinoma HCT 116 cells = 3.6 nM) and a broad spectrum of antitumor activity including paclitaxel-resistant tumors; activity was highly correlated with the degree of tubulin polymerization in peripheral blood mononuclear cells. A phase I clinical trial showed increased tubulin polymerization at 1 and 6 h postdose and a dose-independent pharmacokinetic profile following a 1-h infusion every 3 weeks, 50 mg/m² being the maximum tolerated and recommended dose for further trials; evidence of antitumor activity was seen.

SOURCE – Bristol-Myers Squibb.**REFERENCES**

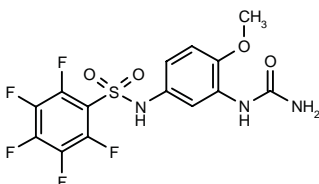
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5. Lee, F.Y.F. et al. *Preclinical pharmacology of the epothilone B analog BMS-247550 - An epothilone analog possessing potent activity against paclitaxel and resistant human tumors.* Clin Cancer Res 2000, 6(Suppl.): Abst 573.
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T-900607***287750**

N-(4-Methoxy-3-ureidophenyl)-2,3,4,5,6-pentafluorobenzenesulfonamide

N-[2-Methoxy-4-(2,3,4,5,6-pentafluorobenzenesulfonamido)phenyl]urea

T-607



C14 H10 F5 N3 O4 S; Mol wt: 411.3060

ACTION – Antineoplastic agent, a derivative of the irreversible β -tubulin-binding agent T-138067, with comparable broad-spectrum cytotoxic activity in the NCI panel of 60 human tumor cell lines including cell lines expressing the multidrug resistance (MDR) phenotype such as human breast carcinoma MCF-7/ADR cells. *In vivo*, like T-138067, compound exhibited strong antitumor activity in the human mammary carcinoma MX-1 xenograft model in mice. However, owing to its decreased lipophilicity compared to the parent compound, T-900607 exhibited poor CNS penetration in mice, giving much less brain tubulin modification and reduced neurotoxicity. Compound is undergoing phase I trials.

SOURCE – Tularik.

REFERENCES

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5. Schwendner, S.W. et al. *Efficacy of combination therapy with the tubulin binding agent, T900607, against MX-1 human mammary tumor xenografts in mice.* Proc Amer Assoc Cancer Res 2000, 41: Abst 1914.

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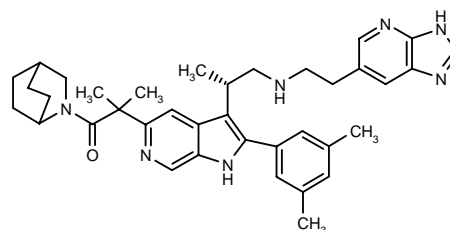
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*Identified compound **287750** Drug Data Rep 2000, 022(07): 0651.

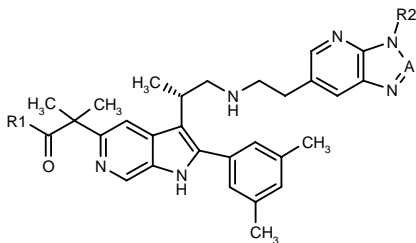
HORMONAL AGENTS**294681**

1-(2-Azabicyclo[2.2.2]oct-2-yl)-2-[2-(3,5-dimethylphenyl)-3-[2-[2-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)ethylamino]-1(*S*)-methylethyl]-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl]-2-methylpropan-1-one



C37 H45 N7 O; Mol wt: 603.8105

ACTION – Gonadotropin-releasing hormone (GnRH or LHRH) antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as adjunctive treatment of growth hormone deficiency, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed 6-azaindole compounds are:



Compound	R1	R2	A	Formula
294682	2-azabicyclo[2.2.2]oct-2-yl	Me	CH	C ₃₈ H ₄₇ N ₇ O
294683	2-azabicyclo[2.2.2]oct-2-yl	H	N	C ₃₈ H ₄₄ N ₈ O
294684	7-azabicyclo[2.2.1]hept-7-yl	H	CH	C ₃₆ H ₄₃ N ₇ O
294685	7-azabicyclo[2.2.1]hept-7-yl	Me	CH	C ₃₇ H ₄₅ N ₇ O
294686	7-azabicyclo[2.2.1]hept-7-yl	H	N	C ₃₆ H ₄₂ N ₈ O

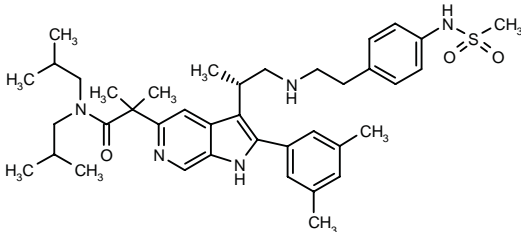
SOURCE – Merck & Co.

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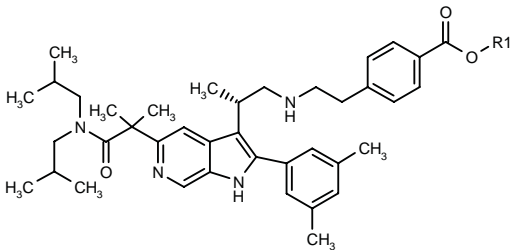
294687

N,N-(Diisobutyl)-2-[2-(3,5-dimethylphenyl)-3-[1(*S*)-methyl-2-[2-[4-(methylsulfonamido)phenyl]ethylamino]ethyl]-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl]-2-methylpropionamide



C39 H55 N5 O3 S; Mol wt: 673.9615

ACTION – Gonadotropin-releasing hormone (GnRH or LHRH) antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as adjunctive treatment of growth hormone deficiency, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed 6-azaindole compounds are:



Compound	R1	Formula
294688	H	C ₃₉ H ₅₂ N ₄ O ₃
294689	Me	C ₄₀ H ₅₄ N ₄ O ₃

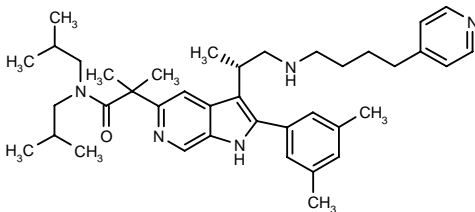
SOURCE – Merck & Co.

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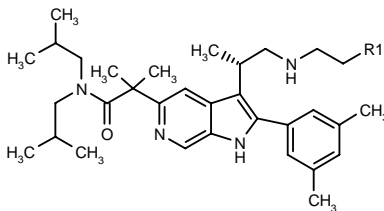
294690

N,N-(Diisobutyl)-2-[2-(3,5-dimethylphenyl)-3-[1(*S*)-methyl-2-[4-(4-pyridyl)butylamino]ethyl]-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl]-2-methylpropionamide



C39 H55 N5 O; Mol wt: 609.8975

ACTION – Gonadotropin-releasing hormone (GnRH or LHRH) antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as adjunctive treatment of growth hormone deficiency, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed 6-azaindole compounds are:



Compound	R1	Formula
294691	4-Pyr-CH2	C ₃₈ H ₅₃ N ₅ O
294692	4-Pyr	C ₃₇ H ₅₁ N ₅ O
294693	2-Me-1-oxido-4-Pyr	C ₃₈ H ₅₃ N ₅ O ₂
294695	2-Me-1-oxido-4-Pyr-CH2	C ₃₉ H ₅₅ N ₅ O ₂
294696	5-benzotriazolyl	C ₃₈ H ₅₁ N ₇ O
294697	5-benzotriazolyl-CH2	C ₃₉ H ₅₃ N ₇ O
294698	1-Me-6-oxo-1,6-dihydro-3-Pyr	C ₃₈ H ₅₃ N ₅ O ₂

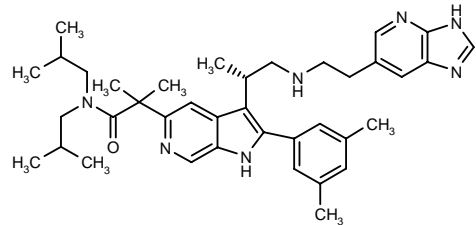
SOURCE – Merck & Co.

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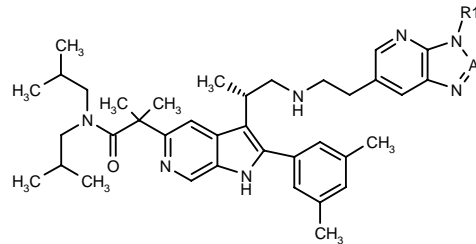
294702

N,N-(Diisobutyl)-2-[2-(3,5-dimethylphenyl)-3-[2-[2-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)ethylamino]-1(*S*)-methylethyl]-1*H*-pyrrolo[2,3-*c*]pyridin-5-yl]-2-methylpropionamide



C38 H51 N7 O; Mol wt: 621.8689

ACTION – Gonadotropin-releasing hormone (GnRH or LHRH) antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as adjunctive treatment of growth hormone deficiency, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed 6-azaindole compounds are:



Compound	R1	A	Formula
294703	Me	CH	C ₃₉ H ₅₃ N ₇ O
294704	H	N	C ₃₇ H ₅₀ N ₆ O

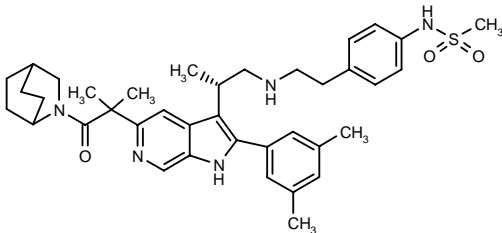
SOURCE – Merck & Co.

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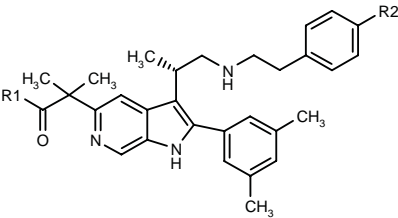
294705

N-[4-[2-[2(*S*)-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-pyrrolo-[2,3-*c*]pyridin-3-yl]propylamino]ethyl]phenyl]methane-sulfonamide



C38 H49 N5 O3 S; Mol wt: 655.9031

ACTION – Gonadotropin-releasing hormone (GnRH or LHRH) antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as adjunctive treatment of growth hormone deficiency, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed 6-azaindole compounds are:



Compound	R1	R2	Formula
294706	2-azabicyclo[2.2.2]oct-2-yl	CO ₂ H	C ₃₈ H ₄₆ N ₄ O ₃
294707	2-azabicyclo[2.2.2]oct-2-yl	CO ₂ Me	C ₃₉ H ₄₈ N ₄ O ₃
294708	7-azabicyclo[2.2.1]hept-7-yl	NHSO ₂ Me	C ₃₇ H ₄₇ N ₆ O ₃ S
294709	7-azabicyclo[2.2.1]hept-7-yl	CO ₂ H	C ₃₇ H ₄₄ N ₄ O ₃
294710	7-azabicyclo[2.2.1]hept-7-yl	CO ₂ Me	C ₃₈ H ₄₆ N ₄ O ₃

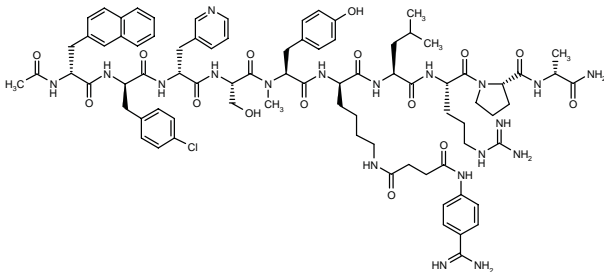
SOURCE – Merck & Co.

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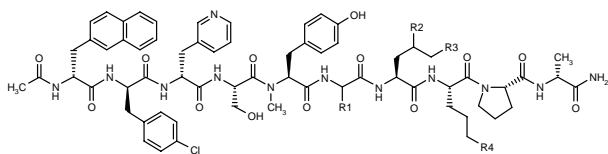
295010

Acetyl-D-3-(2-naphthyl)alanyl-D-4-chlorophenylalanyl-D-3-(3-pyridyl)alanyl-L-seryl-L-(*N*-methyl)tyrosyl-D-[*N*⁶-[4-(4-amidinophenylamino)succinyl]]lysyl-L-leucyl-L-arginyl-L-prolyl-D-alaninamide

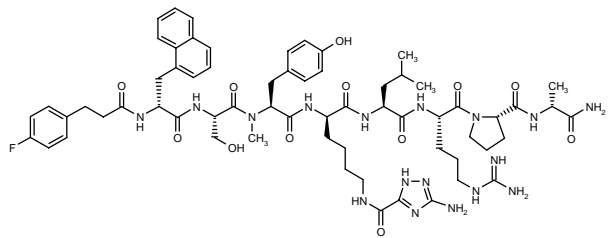


C82 H106 Cl N19 O15; Mol wt: 1633.3100

ACTION – Luteinizing hormone-releasing hormone (LHRH) antagonist reported to exhibit increased enzymatic stability and improved water solubility, potentially useful for the treatment of hormone-dependent tumors, particularly prostate cancer and breast cancer, as well as for the treatment of hormone-mediated non-malignant diseases. Activity was evaluated *in vitro* in a binding assay ($K_D = 154$ pM in Ltk- cells transfected with the human LHRH receptor vs. $K_D = 154$ pM for cetrorelix) and in a functional assay using cells expressing the human LHRH receptor and a luciferase reporter gene ($IC_{50} = 492$ pM vs. 198 pM for cetrorelix). Other exemplified compounds from this series of peptides containing *N*-methylated amino acid building blocks include the following:



Compound	R1	R2	R3	R4	Formula
295011	(S)-(CH2)4NHCONH2	H	Me	NH-C(=NH)NH2	C ₇₂ H ₉₆ ClN ₁₇ O ₁₄
295012	(R)-4-[NH2C(=NH)]-PhNH-COCH2CH2CONH(CH2)4	Me	H	i-PrNHCH2	C ₈₅ H ₁₁₂ ClN ₁₇ O ₁₅



295013: C64 H86 F N17 O12

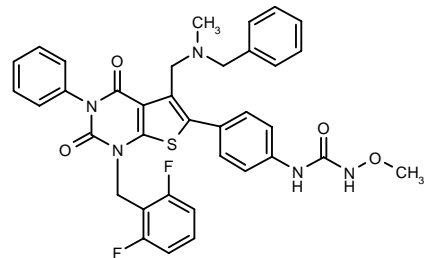
SOURCE – Asta Medica.

REFERENCES

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295240

N-[4-[5-(*N*-Benzyl-*N*-methylaminomethyl)-1-(2,6-difluorobenzyl)-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl]phenyl]-*N'*-methoxyurea



C36 H31 F2 N5 O4 S; Mol wt: 667.7339

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist reported to exhibit good oral absorption, excellent stability and low toxicity. Compound inhibited [¹²⁵I]-leuporelin binding in CHO cells expressing the human GnRH receptor with an IC_{50} value of 0.0001 μ M. In addition, it significantly decreased plasma luteinizing hormone (LH) levels in castrated male cynomolgus monkeys when given at 30 mg/kg p.o. Potentially useful in the prevention and treatment of sex hormone-dependent diseases including sex hormone-dependent cancers, prostatic hypertrophy, endometriosis, precocious puberty and amenorrhea, as well as for birth control and for modulating the menstrual cycle. A specifically claimed compound from a series of thienopyrimidine derivatives.

SOURCE – Takeda.

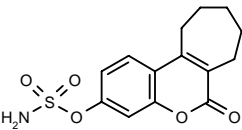
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667COUMATE

296052

Sulfamic acid 6-oxo-6,7,8,9,10,11-hexahydrocyclohepta-[c]-1-benzopyran-3-yl ester



C14 H15 N O5 S; Mol wt: 309.3405

ACTION – Potent, orally active and site-directed steroid sulfatase inhibitor for the treatment of hormone-dependent breast cancer in postmenopausal women. This tricyclic coumarin sulfamate was found to strongly inhibit estrone sulfatase ($IC_{50} = 8$ nM) and DEHA-sulfatase, being 3- and 25-fold more potent than EMATE, respectively. Unlike EMATE, compound is devoid of estrogenic activity. *In vivo*, it inhibited E1 sulfatase activity and the growth of estrogen sulfate-stimulated NMU-induced mammary tumors. A phase I trial is planned to evaluate its efficacy as a treatment for hormone-dependent breast cancer.

SOURCES – University of Bath, Bath (GB); Imperial College of Science, Technology and Medicine, London (GB).

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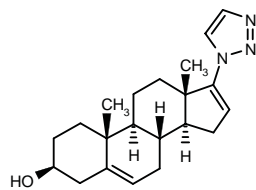
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VN/87-1

261757

3β-Hydroxy-17-(1*H*-1,2,3-triazol-1-yl)androsta-5,16-diene



C21 H29 N3 O; Mol wt: 339.4801

ACTION – Steroidal inhibitor of human testicular 17α-hydroxylase/C_{17,20}-lyase (P45017α; IC₅₀ = 7.97 nM) devoid of activity against 5α-reductase up to 10 μM. Compound exhibited strong antiandrogenic activity in cultured prostate cancer LNCaP cells, where it completely inhibited the proliferative effect of testosterone stimulation at a concentration of 1 μM. In immunodeficient mice bearing LNCaP tumor xenografts, compound was as effective as finasteride in inhibiting tumor growth and this inhibitory effect was similar to castration. Pharmacokinetic studies in mice indicated that compound is well absorbed after s.c. administration and less so after the oral route, with respective absolute bioavailabilities of 60 and 11%. Potentially useful for the treatment of prostate cancer.

SOURCE – University of Maryland, Baltimore, MD (US).

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2. Grigoryev, D.N. et al. Effects of new 17α-hydroxylase/C17,20-lyase inhibitors on LNCaP prostate cancer cell growth in vitro and in vivo. Br J Cancer 2000, 81(4): 622.

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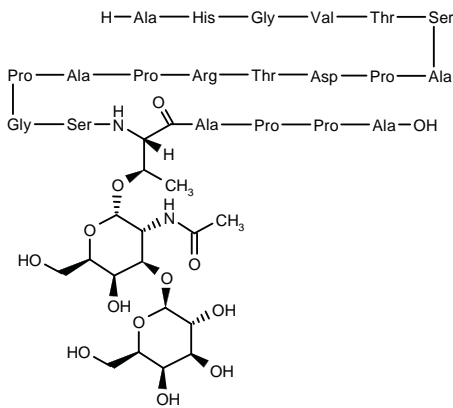
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CANCER IMMUNOTHERAPY

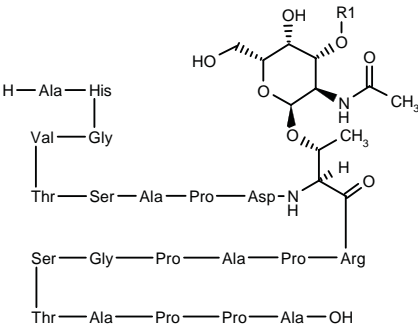
294449

L-Alanyl-L-histidyl-glycyl-L-valyl-L-threonyl-L-seryl-L-alanyl-L-prolyl-L-aspartyl-L-threonyl-L-arginyl-L-prolyl-L-alanyl-L-prolyl-glycyl-L-seryl-3-*O*-[2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-α-D-galactopyranosyl]-L-threonyl-L-alanyl-L-prolyl-L-prolyl-L-alanine



C97 H155 N27 O39; Mol wt: 2323.4410

ACTION – Immunomodulating glycopeptide that causes superproliferation of T-cells, as demonstrated *in vitro* using peripheral blood lymphocytes from healthy volunteers and breast cancer patients, potentially useful for the treatment or diagnosis of cancer. Compound may be used to treat cells both *in vitro* and *ex vivo*, and also as a vaccine adjuvant. Other exemplified glycopeptides are:



Compound	R1	Formula
294451	beta-D-galactopyranosyl	C ₉₇ H ₁₅₅ N ₂₇ O ₃₉
294452	H	C ₉₁ H ₁₄₅ N ₂₇ O ₃₄

SOURCE – Imperial Cancer Research Technology.

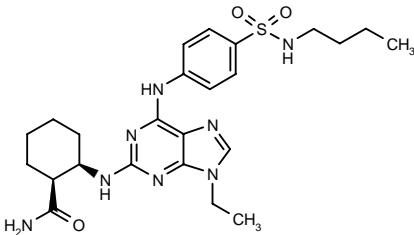
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INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

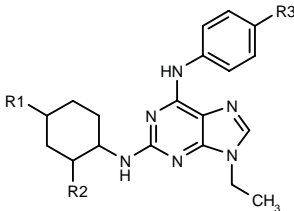
294043

cis-2-[6-[4-(*N*-Butylsulfamoyl)phenylamino]-9-ethyl-9*H*-purin-2-ylamino]cyclohexanecarboxamide

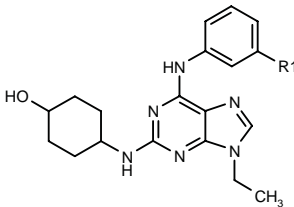


C24 H34 N8 O3 S; Mol wt: 514.6516

ACTION – An inhibitor of p34^{cdc2}/cyclin B^{cdc13} kinase and protein tyrosine kinase pp60^{c-src}, with potential in the treatment of hyperproliferative diseases such as cancer and psoriasis, as well as diseases that respond to inhibition of pp60^{c-src} activity, particularly osteoporosis. Other specifically claimed compounds from this series of 2-amino-6-anilinopurines include the following:



Compound	R1	R2	R3	Isomer	Formula
294044	H	CONH2	1-Pip-SO2	cis	C ₂₅ H ₃₄ N ₈ O ₃ S
294045	OH	H	cyclohexyl-N(Me)SO2	trans	C ₂₆ H ₃₇ N ₇ O ₃ S
294046	OH	H	i-BuCH2NHSO2	trans	C ₂₄ H ₃₅ N ₇ O ₃ S
294048	OH	H	4-(4-morpholinyl)-PhNHSO2	trans	C ₂₉ H ₃₆ N ₈ O ₄ S
294049	OH	H	SO2NHPr	trans	C ₂₂ H ₃₁ N ₇ O ₃ S
294051	OH	H	SO2N(Bu)2	trans	C ₂₇ H ₄₁ N ₇ O ₃ S
294054	OH	H	i-BuOCONH	trans	C ₂₄ H ₃₃ N ₇ O ₃



Compound	R1	Isomer	Formula
294053	4-Me-Ph-CH2NHCO	trans	C ₂₈ H ₃₃ N ₇ O ₂
294055	4-Me-Ph-ethynylene-CONH	trans	C ₂₉ H ₃₁ N ₇ O ₂
294056	t-Bu-ethynylene-CONH		C ₂₆ H ₃₃ N ₇ O ₂

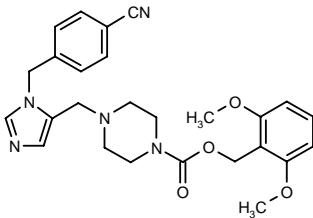
SOURCE – Novartis.

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1. Imbach, P. et al. (Novartis AG) *2-Amino-6-anilino-purines and their use as medicaments*. WO 0049018.

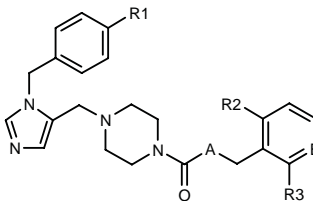
294440

4-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]piperazine-1-carboxylic acid 2,6-dimethoxybenzyl ester



C26 H29 N5 O4; Mol wt: 475.5461

ACTION – Inhibitor of protein prenyltransferases, particularly protein geranylgeranyltransferase type I and the prenylation of the oncogene protein Ras, potentially useful for the treatment of cancer including but not limited to colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemia and brain tumors. The angiogenesis-inhibitory activity of this compound makes it potentially useful for the treatment of certain forms of vision deficit related to retinal vascularization. It is also indicated for the treatment of benign proliferative disorders and hepatitis delta infections, and for the prevention of restenosis and polycystic kidney disease. Other specifically claimed piperazine-containing compounds are:



Compound	R1	R2	R3	A	B	Formula
294441	CN	Me	Me	O	CH	C ₂₆ H ₂₉ N ₅ O ₂
294442	Me	Me	Me	O	CH	C ₂₆ H ₃₂ N ₄ O ₂
294443	CN	H	OEt	O	CH	C ₂₆ H ₂₉ N ₅ O ₃
294444	CN	H	OEt	NH	CH	C ₂₆ H ₃₀ N ₆ O ₂
294445	CN	H	OEt	O	N	C ₂₅ H ₂₈ N ₆ O ₃

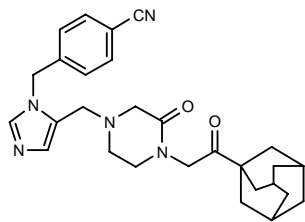
SOURCE – Merck & Co.

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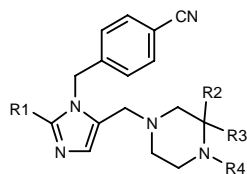
294468

4-[5-[4-[2-(1-Adamantyl)-2-oxoethyl]-3-oxopiperazin-1-ylmethyl]-1 *H*-imidazol-1-ylmethyl]benzonitrile



C28 H33 N5 O2; Mol wt: 471.6017

ACTION – Inhibitor of protein prenyltransferases, particularly protein geranylgeranyltransferase type I and the prenylation of the oncogene protein Ras, potentially useful for the treatment of cancer including but not limited to colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemia and brain tumors. The angiogenesis-inhibitory activity of this compound makes it potentially useful for the treatment of certain forms of vision deficit related to retinal vascularization. It is also indicated for the treatment of benign proliferative disorders and hepatitis delta infections, and for the prevention of restenosis and polycystic kidney disease. Other specifically claimed piperazine-containing compounds are:



Compound	R1	R2	R3	R4	Formula
294470	H	-O-		1-adamantyl-CH(OH)CH2	C ₂₈ H ₃₅ N ₅ O ₂
294471	H	-O-		1-adamantyl-CH(OAc)CH2	C ₃₀ H ₃₇ N ₅ O ₃
294472	H	H	H	1-adamantyl-NHCO	C ₂₇ H ₃₄ N ₆ O
294473	H	H	H	1-adamantyl-CO	C ₂₇ H ₃₃ N ₅ O
294475	H	H	H	1-adamantyl-CH2	C ₂₇ H ₃₅ N ₅
294476	H	-O-		1-adamantyl-CH2CH2	C ₂₈ H ₃₅ N ₅ O
294477	H	-O-		1-adamantyl-CH2	C ₂₇ H ₃₃ N ₅ O
294478	H	H	H	bicyclo[2.2.1]hept-2-yl-CH2OCO	C ₂₅ H ₃₁ N ₅ O ₂
294479	H	H	H	bicyclo[2.2.2]oct-2-yl-CO	C ₂₅ H ₃₁ N ₅ O
294480	H	H	H	bicyclo[2.2.1]hept-2-yl-CO	C ₂₄ H ₂₉ N ₅ O
294481	H	H	H	3,6,6-(Me)3-bicyclo[3.1.1]hept-2-yl-CO	C ₂₇ H ₃₅ N ₅ O
294482	Me	H	H	1-adamantyl-NHCO	C ₂₈ H ₃₆ N ₆ O

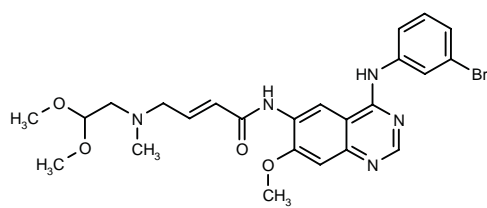
SOURCE – Merck & Co.

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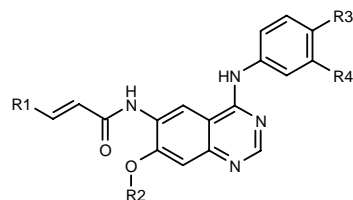
294500

N-[4-(3-Bromophenylamino)-7-methoxyquinazolin-6-yl]-4-[*N*-(2,2-dimethoxyethyl)-*N*-methylamino]-2-butenamide



C24 H28 Br N5 O4; Mol wt: 530.4202

ACTION – Inhibitor of signal transduction mediated by tyrosine kinases, particularly epidermal growth factor (EGF) receptor kinase. It inhibited EGF-dependent proliferation of cells expressing the human EGF receptor with an IC₅₀ value of 1.8 nM. Potentially useful for the treatment of benign or malignant tumors, particularly those of epithelial and neuroepithelial origin, inflammatory airways diseases, polyps, and gastrointestinal tract, bile duct and gallbladder disorders. Other exemplified compounds within this series of 4-amino-quinazoline and quinoline derivatives are:



Compound	R1	R2	R3	R4	Formula
294501	H	4-(EtOCOCH2)-1-Piz-(CH2)3	H	Br	C ₂₈ H ₃₃ BrN ₆ O ₄
294502	2-EtO-4-morpholinyl-CH2	Me	H	Br	C ₂₅ H ₂₈ BrN ₅ O ₄
294503	4-(EtOCOCH2)-1-Piz-CH2	cyclobutyl	F	Cl	C ₃₀ H ₃₄ ClFN ₆ O ₄
294504	-CH2-L-Pro-OMe	cyclopropyl-CH2	F	Cl	C ₂₈ H ₂₉ ClFN ₅ O ₄

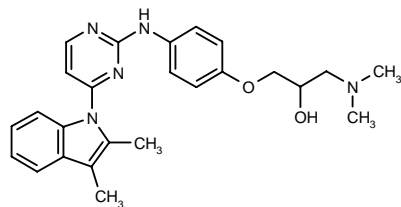
SOURCE – Boehringer Ingelheim.

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294715

1-(Dimethylamino)-3-[4-[4-(2,3-dimethyl-1 *H*-indol-1-yl)pyrimidin-2-ylamino]phenoxy]propan-2-ol



C25 H29 N5 O2; Mol wt: 431.5371

ACTION – Antiproliferative agent that acts by inhibiting the cell cycle kinases CDK2, CDK4 (IC_{50} = 0.02 μ M) and CDK6, and the focal adhesion kinase FAK, expected to possess anticancer activity, particularly against solid tumors and leukemias.

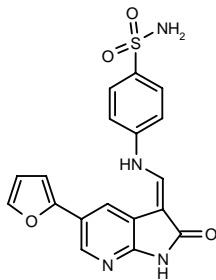
SOURCE – AstraZeneca.

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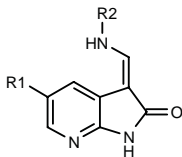
294964

4-[5-(2-Furyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylidenemethylamino]benzenesulfonamide



C18 H14 N4 O4 S; Mol wt: 382.3986

ACTION – An inhibitor of cyclin-dependent kinases, especially CDK2, with potential in the treatment of cancer, restenosis, psoriasis, actinic keratosis and alopecia associated with cancer chemotherapy. *In vitro*, compound inhibited CDK2 with an IC_{50} value in the range of 0.01-0.1 μ M, while exhibiting IC_{50} values of 0.1-10 μ M for inhibition of c-fms and of 1.0-10 μ M for inhibition of VEGFR2. Other exemplified compounds from this series of substituted aza-oxindole derivatives include the following:



Compound	R1	R2	Formula
294965	Br	4-(NH2SO2)-Ph	C ₁₄ H ₁₁ BrN ₄ O ₃ S
294966	Br	6-indazolyl	C ₁₅ H ₁₀ BrN ₅ O
294967	Br	6-quinolyl	C ₁₇ H ₁₁ BrN ₄ O
294968	CO2Et	4-(NH2SO2)-Ph	C ₁₇ H ₁₆ N ₄ O ₃ S

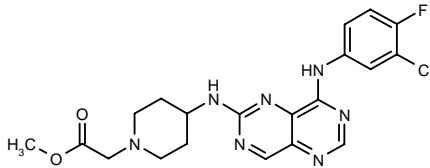
SOURCE – GlaxoSmithKline.

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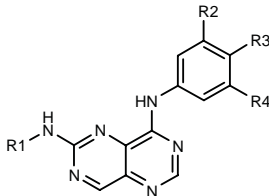
295014

2-[4-[8-(3-Chloro-4-fluorophenylamino)pyrimido[5,4-*d*]pyrimidin-2-ylamino]piperidin-1-yl]acetic acid methyl ester



C20 H21 Cl F N7 O2; Mol wt: 445.8839

ACTION – Inhibitor of epidermal growth factor (EGF) receptor-mediated signal transduction, as demonstrated by inhibition of EGF-dependent proliferation of cells expressing the human EGF receptor (IC_{50} = 15 nM). Potentially useful for the treatment of tumors, particularly those of epithelial and neuroepithelial origin, as well as inflammatory airways diseases and gastrointestinal tract, bile duct and gallbladder disorders. Other specifically claimed bicyclic heterocycles are:



Compound	R1	R2	R3	R4	Formula
295015	trans-4-[MeOCOCH2N(Me)]-cyclohexyl	H	F	Cl	C ₂₂ H ₂₅ ClFN ₇ O ₂
295016	1-(MeOCOCH2)-4-Pip	H	H	Br	C ₂₀ H ₂₂ BrN ₇ O ₂
295017	1-(MeOCOCH2)-4-Pip	H	H	Cl	C ₂₀ H ₂₂ ClN ₇ O ₂
295018	1-(MeOCOCH2)-4-Pip	H	H	Me	C ₂₁ H ₂₅ N ₇ O ₂
295019	1-(MeOCOCH2)-4-Pip	Cl	NH2	Cl	C ₂₀ H ₂₂ Cl ₂ N ₈ O ₂
295020	1-(MeOCOCH2)-4-Pip	Br	NH2	Br	C ₂₀ H ₂₂ Br ₂ N ₈ O ₂
295021	1-(MeOCOCH2)-4-Pip	H	-NHCH=CH-		C ₂₂ H ₂₄ N ₈ O ₂
295022	trans-4-[N(CH2CO2Et)2]-cyclohexyl	H	F	Cl	C ₂₆ H ₃₁ ClFN ₇ O ₄
295023	trans-4-[N(CH2CO2Me)2]-cyclohexyl	H	F	Cl	C ₂₄ H ₂₇ ClFN ₇ O ₄
295024	trans-4-(MeOCOCH2NH)-cyclohexyl	H	F	Cl	C ₂₁ H ₂₃ ClFN ₇ O ₂
295025	1-[(CO2Me)2CH]-4-Pip	H	H	Br	C ₂₂ H ₂₄ BrN ₇ O ₄
295026	1-(MeOCOCH2)-3-Pip	H	H	Br	C ₂₀ H ₂₂ BrN ₇ O ₂
295027	1-[(CO2Me)2CH]-4-Pip	H	F	Cl	C ₂₂ H ₂₃ ClFN ₇ O ₄
295028	1-[(EtO)2POCH2]-4-Pip	H	H	Br	C ₂₂ H ₂₉ BrN ₇ O ₃ P
295029	1-[(EtO)(Me)POCH2]-4-Pip	H	H	Br	C ₂₁ H ₂₇ BrN ₇ O ₂ P

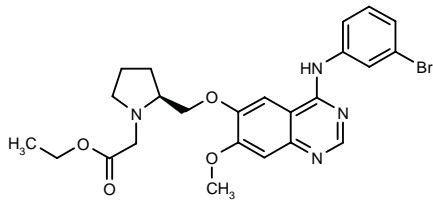
SOURCE – Boehringer Ingelheim.

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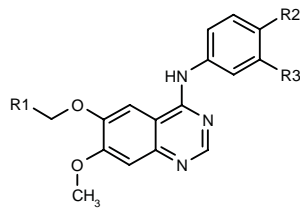
295032

2-[2(*S*)-[4-(3-Bromophenylamino)-7-methoxyquinazolin-6-yloxymethyl]pyrrolidin-1-yl]acetic acid ethyl ester



C24 H27 Br N4 O4; Mol wt: 515.4053

ACTION – Inhibitor of epidermal growth factor (EGF) receptor-mediated signal transduction, as demonstrated by inhibition of EGF-dependent proliferation of cells expressing the human EGF receptor (IC₅₀ = 20 nM). Potentially useful for the treatment of tumors, particularly those of epithelial and neuroepithelial origin, as well as inflammatory airways diseases and gastrointestinal tract, bile duct and gallbladder disorders. Other specifically claimed bicyclic heterocycles are:



Compound	R1	R2	R3	Formula
295033	4-(MeOCOCH2)-1-Piz-CH2CH2	F	Cl	C ₂₅ H ₂₉ ClF ₂ N ₅ O ₄
295034	4-(EtOCOCH2)-1-Piz-CH2	H	Br	C ₂₅ H ₃₀ BrN ₅ O ₄
295035	-CH2CH2-L-Pro-OMe	H	Br	C ₂₄ H ₂₇ BrN ₄ O ₄
295036	4-(EtOCOCH2)-1-Piz-CH2CH(OH)	H	Br	C ₂₆ H ₃₂ BrN ₅ O ₅
295037	4-[MeOCOCH2CH(CO2Me)]-1-Piz-CH2	H	Br	C ₂₇ H ₃₂ BrN ₅ O ₆

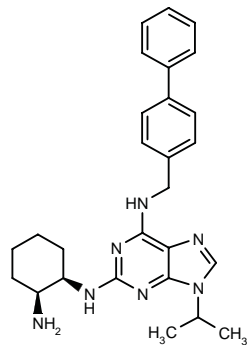
SOURCE – Boehringer Ingelheim.

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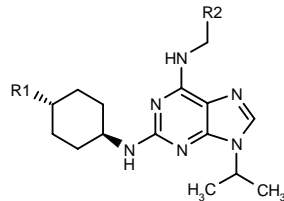
295047

cis-*N*²-(2-Aminocyclohexyl)-*N*⁶-(biphenyl-4-ylmethyl)-9-isopropyl-9*H*-purine-2,6-diamine



C27 H33 N7; Mol wt: 455.6067

ACTION – A cyclin/cyclin-dependent kinase (CDK) inhibitor, potentially useful for the treatment of cell proliferative disorders, particularly rheumatoid arthritis, lupus, type 1 diabetes, multiple sclerosis, cancer, restenosis and gout. *In vitro*, compound exhibited IC₅₀ values of 5, 2 and 6 μM against cyclin A/CDK2, cyclin E/CDK2 and cyclin B/CDK1, respectively, and was found to inhibit the growth of HeLa cells with a GI₅₀ value of 0.01-0.2 μM. In addition, it exhibited potent cytotoxicity in the NCI 60 panel of human tumor cell lines, with GI₅₀ values in the range of < 0.01-0.24 μM. Other exemplified compounds from this series of 6-substituted biaryl purine derivatives include the following:



Compound	R1	R2	Formula
295048	NH2	4-Ph-Ph	C ₂₇ H ₃₃ N ₇
295049	NHAc	4-Ph-Ph	C ₂₉ H ₃₅ N ₇ O
295050	NHAc	4-(2-Pyr)-Ph	C ₂₈ H ₃₄ N ₈ O
295051	NHAc	6-Ph-3-Pyr	C ₂₈ H ₃₄ N ₈ O
295052	NH2	4-(3-thienyl)-Ph	C ₂₅ H ₃₁ N ₇ S
295054	OH	4-Ph-Ph	C ₂₇ H ₃₂ N ₆ O
295057	NH2	4-(2-Pyr)-Ph	C ₂₆ H ₃₂ N ₈

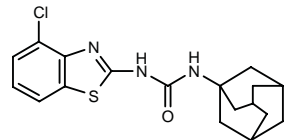
SOURCE – Albany Molecular Research.

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295241

N-(1-Adamantyl)-*N*'-(4-chlorobenzothiazol-2-yl)urea



C18 H20 Cl N3 O S; Mol wt: 361.8950

ACTION – MEK inhibitor potentially useful for the treatment of autoimmune diseases and proliferative disorders such as arthritis, cancer, psoriasis, restenosis and atherosclerosis. It is also expected to be of use as a radiosensitizer for the therapy of solid tumors.

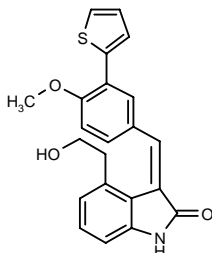
SOURCE – DuPont Pharmaceuticals.

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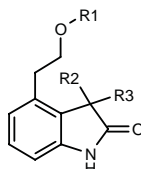
295246

4-(2-Hydroxyethyl)-3-[4-methoxy-3-(2-thienyl)benzylidene]-2,3-dihydro-1*H*-indol-2-one



C22 H19 N O3 S; Mol wt: 377.4621

ACTION – Agent for the treatment and prevention of cancer, as well as immunological, hyperproliferative, cardiovascular and inflammatory disorders, restenosis, fibrosis, psoriasis, osteoarthritis, rheumatoid arthritis, atherosclerosis, diabetes and angiogenesis, a representative compound from a series of indolinone derivatives that act by inhibiting protein kinases. *In vitro*, compound was found to inhibit HER2 kinase activity with an IC₅₀ value of 8.5 μ M, while IC₅₀ values for platelet-derived growth factor (PDGF) receptor and epithelial growth factor (EGF) receptor kinases were > 100 μ M. This compound also potently inhibited the growth of human ovarian carcinoma SK-OV-3 and human epidermoid carcinoma A-431 cells *in vitro*, with respective IC₅₀ values of 1.5 and 2.5 μ M. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
295247	3- <i>i</i> -Pr-Ph	H	H	C ₁₉ H ₂₁ NO ₂
295248	2- <i>i</i> -Pr-Ph	H	H	C ₁₉ H ₂₁ NO ₂
295249	H	-CH(6-Me-2-Pyr)		C ₁₇ H ₁₈ N ₂ O ₂

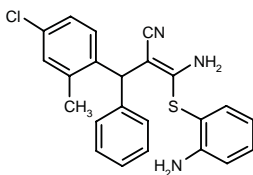
SOURCE – Sugen (Pharmacia).

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1. Tang, P.C. et al. (Sugen, Inc.) *Indolinone cpds. as kinase inhibitors*. WO 0056709.

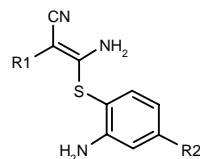
295270

3-Amino-3-(2-aminophenylsulfanyl)-2-[1-(4-chloro-2-methylphenyl)-1-phenylmethyl]-2(*E*)-propenenitrile



C23 H20 Cl N3 S; Mol wt: 405.9510

ACTION – Dual MEK1 and MEK2 inhibitor, potentially useful for the treatment of autoimmune diseases and proliferative disorders such as arthritis, cancer, psoriasis, restenosis and atherosclerosis. It is also expected to be of use as a radiosensitizer for the therapy of solid tumors. Other specifically claimed acrylonitriles are:



Compound	R1	R2	Formula
295271	2-Me-3-[4-Pyr-CH(OH)]-Ph	H	C ₂₂ H ₂₀ N ₄ OS
295274	2-Me-3-[(F)5-Ph-CH(OH)]-Ph	H	C ₂₃ H ₁₆ F ₅ N ₃ OS
295276	3-[3-CN-Ph-CH(OH)]-Ph	H	C ₂₃ H ₁₈ N ₄ OS
295279	3-[2,4-(Me)2-Ph-CH(OH)]-Ph	H	C ₂₄ H ₂₃ N ₃ OS
295280	1-Naph	NH2	C ₁₉ H ₁₆ N ₄ S
295284	1-Me-2-pyrrolyl-CH(Ph)	H	C ₂₁ H ₂₀ N ₄ S
295286	3-[3-Me-2-Pyr-CH(OH)]-Ph	H	C ₂₂ H ₂₀ N ₄ OS
295287	2-CF3-Ph	H	C ₁₆ H ₁₂ F ₃ N ₃ S
295289	3-Ph-Ph	H	C ₂₁ H ₁₇ N ₃ S

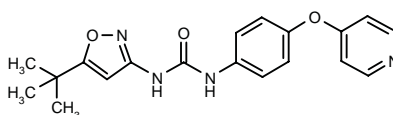
SOURCE – DuPont Pharmaceuticals.

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295995

N-(5-*tert*-Butylisoxazol-3-yl)-*N*'-[4-(4-pyridyloxy)-phenyl]urea



C19 H20 N4 O3; Mol wt: 352.3920

ACTION – Antineoplastic agent, a selective, orally active Raf kinase inhibitor (IC₅₀ = 230 nM) that does not directly inhibit MEK1 or ERK1 activity *in vitro* (IC₅₀ = 9500 and > 10,000 nM, respectively) but inhibits Raf kinase-mediated activation of both MEK1 and ERK1 in human epidermoid carcinoma A-431 cells. At concentrations required to inhibit Raf kinase, compound inhibited anchorage-dependent and -independent growth of human colon carcinoma HCT 116 cells. In mice, compound exhibited strong and dose-dependent inhibition of the growth of human tumor xenografts containing mutations in the *K-ras* gene, i.e., human colon carcinoma HCT 116 and human pancreatic carcinoma Mia PaCa2 xenografts. It was also active in mice bearing ovarian carcinoma SK-OV-3 xenografts overexpressing the epidermal growth factor (EGF) and HER2 growth factor receptors. Pharmacokinetic experiments in mice demonstrated that compound is rapidly absorbed after oral administration, with a mean half-life of 2.4 h and significant oral bioavailability (about 71%).

SOURCES – Bayer; Onyx.

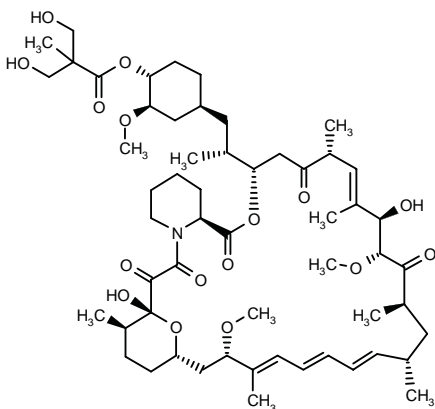
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1. Dumas, J. et al. (Bayer Corp.) *Inhibition of p38 kinase activity using substd. heterocyclic ureas*. WO 9932111.
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3. Eberwein, D. et al. *In vivo activity of a Raf kinase inhibitor in human tumor xenograft models*. Clin Cancer Res 2000, 6(Suppl.): Abst 406.
4. Hibner, B. et al. *Pharmacokinetics of a Raf kinase inhibitor in CD-1 mice after single dose administration*. Clin Cancer Res 2000, 6(Suppl.): Abst 407.
5. Lowinger, T.B. et al. *Discovery of a novel class of potent Raf kinase inhibitors: Structure activity relationships*. Clin Cancer Res 2000, 6(Suppl.): Abst 335.
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CCI-779*

218793

[1R,9S,12S[1'R(1''R,3''R,4''R)],15R,18R,19R,21R,23S,30S,32S,35R]-1,18-Dihydroxy-12-[2-[4-[3-hydroxy-2-(hydroxymethyl)-2-methylpropionyloxy]-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,-23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo-[30.3.1.0(4,9)]hexatriaconta-16(E),24(E),26(E),28(E)-tetraene-2,3,10,14,20-pentaone



C56 H87 N O16; Mol wt: 1030.3100

ACTION – Ester analogue of rapamycin (sirolimus) with antitumor activity but no significant immunosuppressive activity. It inhibits mTOR protein kinase activity and thereby interferes with the translation of several cell cycle-regulatory proteins, resulting in cell growth arrest in the G1 phase of the cell cycle. Compound exhibited growth-inhibitory activity in both *in vitro* ($IC_{50} < 100$ nM) and *in vivo* preclinical models including glioblastomas, prostate, pancreas and breast carcinomas and medulloblastomas. Phase I clinical studies in patients with advanced solid tumors demonstrated that compound was well tolerated at a wide range of i.v. doses, with mild toxicity at doses above 15 mg/m²/week. On the basis of the promising clinical safety and efficacy data, it has progressed to phase II trials.

SOURCE – Wyeth-Ayerst.

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3. Alexandre, J. et al. *Phase I study of CCI-779, a novel rapamycin analog: Preliminary results*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3897.

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6. Hidalgo, M. et al. *A phase I and pharmacological study of CCI-779, a rapamycin ester cell cycle inhibitor*. Ann Oncol 2000, 11(Suppl. 4): Abst 606O.

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10. Raymond, E. et al. *CCI-779, a rapamycin analog with antitumor activity: A phase I study utilizing a weekly schedule*. Proc Am Soc Clin Oncol 2000, 19: Abst 728.

11. Raymond, E. et al. *CCI-779, an ester analogue of rapamycin that interacts with PTEN/PI3 kinase pathways: A phase I study utilizing a weekly intravenous schedule*. Clin Cancer Res 2000, 6(Suppl.): Abst 414.

12. *AHP highlights innovative new products at NYC conference*. DailyDrugNews.com (Daily Essentials) 2000, Oct 31.

13. *CCI-779: a new rapamycin analogue targeting mTOR with a promising clinical profile*. DailyDrugNews.com (Daily Essentials) 2000, Nov 23.

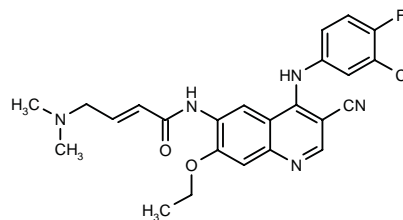
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*Identified compound **218793** (see **216465**) Drug Data Rep 1995, 017(04): 0377.

EKB-569

293935

N-[4-(3-Chloro-4-fluorophenylamino)-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)-2(*E*)-butenamide



C24 H23 Cl F N5 O2; Mol wt: 467.9297

ACTION – Antineoplastic agent found to potently inhibit recombinant epidermal growth factor (EGF) receptor tyrosine kinase ($IC_{50} = 1.33$ nM) and EGF receptor kinase phosphorylation in cells overexpressing the EGF receptor ($IC_{50} = 15$ nM). Compound showed equivalent cytotoxicity against cells overexpressing either the EGF receptor or c-erbB-2 ($IC_{50} = 14-66$ nM and 12-50 nM, respectively) but at least 10-fold higher concentrations were required to inhibit the growth of cells not overexpressing these proteins. *In vivo*, a dose of 10 mg/kg/day p.o. produced 81-82% tumor growth inhibition in murine xenograft models of tumors with high levels of EGF receptor expression such as human epidermoid carcinoma A-431 and a tumor derived from HN-5 cells. Good activity was also seen against tumors overexpressing c-erbB-2, but compound had little or no activity against tumors expressing low levels of these proteins. Its ability to inhibit EGF receptor phosphorylation in tumors was sustained

longer than the plasma levels of drug, indicating irreversible inhibition. In a murine model of human familial adenomatous polyposis, compound in combination with a nonsteroidal antiinflammatory drug (NSAID) was found to reduce colonic polyp formation, indicating potential for the chemoprevention of human colonic neoplasia. Compound is undergoing phase I trials in cancer patients.

SOURCES – Genetics Institute; Wyeth-Ayerst.

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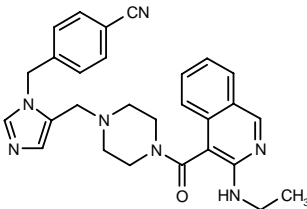
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L-452958

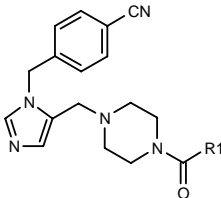
294446

4-[5-[4-[3-(Ethylamino)isoquinolin-4-ylcarbonyl]piperazin-1-ylmethyl]-1*H*-imidazol-1-ylmethyl]benzonitrile



C28 H29 N7 O; Mol wt: 479.5851

ACTION – Inhibitor of protein prenyltransferases, particularly protein geranylgeranyltransferase type I and the prenylation of the oncogene protein Ras, potentially useful for the treatment of cancer including but not limited to colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemia and brain tumors. The angiogenesis-inhibitory activity of this compound makes it potentially useful for the treatment of certain forms of vision deficit related to retinal vascularization. It is also indicated for the treatment of benign proliferative disorders and hepatitis delta infections, and for the prevention of restenosis and polycystic kidney disease. Other specifically claimed piperazine-containing compounds are:



Compound	R1	Formula
294447	3-Me-4-(Me-ethynylene)-Ph	C ₂₇ H ₂₇ N ₅ O
294448	6-N(Et)2-2-Pyr	C ₂₆ H ₃₁ N ₇ O
294450	1-Naph	C ₂₇ H ₂₅ N ₅ O

SOURCE – Merck & Co.

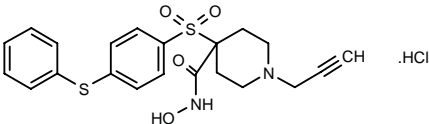
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ANGIOGENESIS INHIBITORS

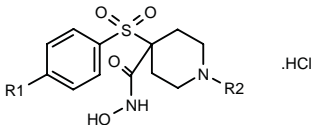
294276

4-[4-(Phenylsulfanyl)phenylsulfonyl]-1-(2-propynyl)-piperidine-4-carboxylic acid hydrochloride



C21 H22 N2 O4 S2 . HCl; Mol wt: 467.0077

ACTION – Selective inhibitor of matrix metalloproteinases such as MMP-2 (gelatinase A), MMP-9 (gelatinase B) and MMP-13 (collagenase 3), while exhibiting substantially less activity at MMP-1 (fibroblast collagenase), with respective IC₅₀ values of 0.2 nM, 1.5 nM and 0.5 nM against recombinant MMP-2, MMP-9 and MMP-13, versus 9000 nM against MMP-1. As such, this compound is useful for inhibiting tumor growth and angiogenesis with reduced side effects, as demonstrated in the corneal micropocket model of angiogenesis in mice, in which 50 and 46% reductions in the area of neovascularization were obtained at 10 and 50 mg/kg p.o. b.i.d., respectively. It demonstrated antitumor activity in mice bearing human prostate adenocarcinoma PC-3 tumors, with an average tumor reduction of 40 and 60% at 10 and 50 mg/kg p.o. b.i.d., respectively. The compound showed a good pharmacokinetic profile when administered to rats at 20 mg/kg p.o. or i.v. Other exemplified aromatic sulfone hydroxamic acids include the following:

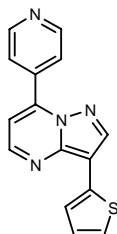


Compound	R1	R2	Formula
294277	OPh	H	C ₁₈ H ₂₀ N ₂ O ₅ S.HCl
294279	1,3-benzodioxol-5-yl-O	ethynyl-CH2	C ₂₂ H ₂₂ N ₂ O ₇ S.HCl
294281	4-F-PhS	ethynyl-CH2	C ₂₁ H ₂₁ FN ₂ O ₄ S ₂ .HCl

SOURCE – Pharmacia.

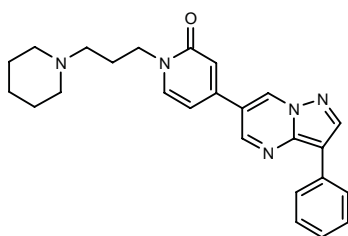
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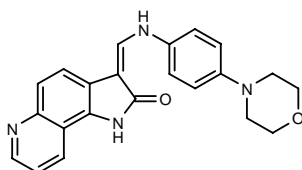
2946797-(4-Pyridyl)-3-(2-thienyl)pyrazolo[1,5-*a*]pyrimidine

C15 H10 N4 S; Mol wt: 278.3380

ACTION – Angiogenesis inhibitor, a tyrosine kinase inhibitor with selectivity for vascular endothelial growth factor (VEGF) kinases. Particularly useful for the treatment of cancers, preferably solid tumors, and ocular diseases such as diabetic retinopathy. Another exemplified compound is:

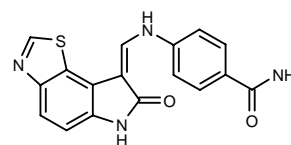
**294680:** C25 H27 N5 O**SOURCE** – Merck & Co.**REFERENCES**

1. Bilodeau, M.T. et al. (Merck & Co., Inc.) Tyrosine kinase inhibitors. WO 0053605.

2951733-[(*Z*)-4-(4-Morpholinyl)phenylaminomethylene]-2,3-dihydro-1*H*-pyrrolo[2,3-*h*]quinolin-2-one

C22 H20 N4 O2; Mol wt: 372.4260

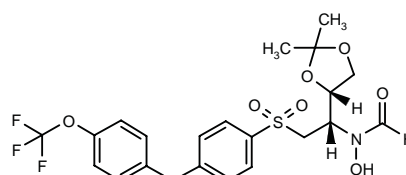
ACTION – Vascular endothelial growth factor VEGFR2 kinase inhibitor (IC_{50} = 11-50 nM) with selectivity over other kinases such as CDK2, Tie-2 and c-fms (IC_{50} > 100 nM). This compound was able to block mitogenesis in endothelial cells, as demonstrated by inhibition of VEGF-stimulated bromovinyldeoxyuridine (BrDU) incorporation into human umbilical vein endothelial cells (HUVEC; IC_{50} = 0.01-0.05 μ M). Its selectivity was demonstrated using basic fibroblast growth factor (bFGF) to stimulate BrDU incorporation (IC_{50} > 5.0 μ M). Potentially useful for the treatment of malignant tumors and other disorders involving abnormal angiogenesis. Another exemplified compound within this series of 3-(anilinomethylene)-oxindoles is:

**295174:** C17 H12 N4 O2 S**SOURCE** – GlaxoSmithKline.**REFERENCES**

1. Glennon, K.C. et al. (Glaxo Group Ltd.) 3-(Anilinomethylene) oxindoles as protein tyrosine kinase and protein serine/threonine kinase inhibitors. WO 0056710.

ABT-518**295748**

N-[1(S)-[2,2-Dimethyl-1,3-dioxolan-4(S)-yl]-2-[4-[4-(trifluoromethoxy)phenoxy]phenylsulfonyl]ethyl]-N-hydroxyformamide



C21 H22 F3 N O8 S; Mol wt: 505.4638

ACTION – Matrix metalloproteinase inhibitor with high selectivity for gelatinase A and gelatinase B (IC_{50} = 0.8 and 0.5 nM, respectively) versus fibroblast collagenase, matrilysin (IC_{50} = 8.9 and 11 μ M, respectively) and other metalloproteinases including thermolysin, leucine aminopeptidase and neprilysin (IC_{50} > 100 μ M). Compound exhibited cytotoxic activity against murine melanoma B16 cells (CC_{50} = 45 μ M) and had no significant effect on cell viability at concentrations up to 45 μ M. *In vivo*, anti-angiogenic activity was seen by inhibition of fibroblast growth factor (FGF)-induced vessel penetration in Matrigel plugs in mice, as well as FGF- and vascular endothelial growth factor (VEGF)-induced corneal neovascularization. ABT-518 given orally at doses of 3-10 and 30 mg/kg demonstrated antitumor activity in murine syngeneic and human xenograft models including murine melanoma B16, human fibrosarcoma HT-1080, human pancreatic carcinoma MiaPaCa and human brain glioma D54. Compound was also active in orthotopic breast and colon tumor models (10-100 mg/kg p.o.). Combination therapy with cytotoxic agents such as paclitaxel or gemcitabine resulted in additive effects on tumor growth.

SOURCE – Abbott.**REFERENCES**

1. Curtin, M.L. et al. (Abbott Laboratories Inc.) Reverse hydroxamate inhibitors of matrix metalloproteinases. WO 0044739.

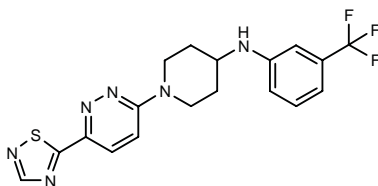
2. Albert, D.H. et al. Preclinical pharmacology of ABT-518, a novel potent inhibitor of gelatinase A and B with anti-tumor activity. Clin Cancer Res 2000, 6(Suppl.): Abst 301.

3. Abbott Laboratories. Merrill Lynch Global Healthcare Conf (Feb 6-8, New York) 2001.

R-123942

295755

N-[1-[6-(1,2,4-Thiadiazol-5-yl)pyridazin-3-yl]piperidin-4-yl]-*N*-[3-(trifluoromethyl)phenyl]amine



C18 H17 F3 N6 S; Mol wt: 406.4343

ACTION – Angiogenesis inhibitor selected from a series of thiadiazole pyridazine analogues, proven to inhibit microvessel growth in isolated rat aortic rings ($IC_{50} = 0.7$ nM) and growth factor-induced angiogenesis in the mouse Matrigel plug assay *in vivo* after oral dosing. Orally administered compound induced significant and dose-dependent (7.5-60 mg/kg b.i.d. for 28 days) inhibition of the growth of primary 3LL Lewis lung tumors in mice and significant antimetastatic activity, without overt toxicity or loss of body weight. The mechanism of antiangiogenic activity of the compound is unclear, and it was devoid of significant effects on proliferation, migration or capillary tube formation of human endothelial cells at concentrations 1,000-fold greater than the *in vitro* IC_{50} in the rat aortic ring assay. Further evaluation in human tumor xenograft models is in progress.

SOURCE – Janssen.

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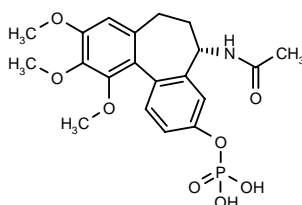
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2. Smets, G. et al. *Characterization of R123942, a novel anti-angiogenic agent, in human endothelial cell assays of proliferation, migration and tube formation*. Clin Cancer Res 2000, 6(Suppl.): Abst 288.
3. Tuman, R. et al. *R123942, a novel thiadiazole pyridazine with potent in vitro and in vivo anti-angiogenic activity*. Clin Cancer Res 2000, 6(Suppl.): Abst 287.

ZD-6126^{2,4,6-13}

271158

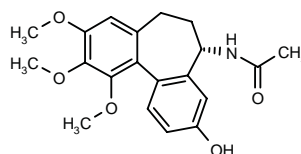
5-(*S*)-Acetamido-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl dihydrogen phosphate

ANG-453



C20 H24 N O8 P; Mol wt: 437.3826

ACTION – Tubulin-binding agent, a phosphate prodrug of *N*-acetylcolchicolin (**ZM-445526**) that produces selective destruction of tumor vasculature via selective inhibition of proliferating endothelial cells. In mice, the phosphate prodrug showed a very short half-life, rapidly releasing free drug ($t_{1/2} < 10$ min). When given as a single i.v. dose of 50-200 mg/kg to athymic mice bearing human lung carcinoma Calu-6, it produced significant tumor necrosis at 24 h, with maximal necrosis of 80-90% of the tumor area. However, a rim of viable tumor cells remained in the periphery of the tumor and induced tumor regrowth after 5 days. Pretreatment with cisplatin 24 h before compound was seen to induce tumor regression and prolong tumor growth delay. In sarcoma KHT-bearing mice, a dose of 150 mg/kg 1 h following various doses of cisplatin induced a strong decrease in cell survival without increasing the bone marrow stem cell toxicity of cisplatin. Also, when compound was given following a single dose of radiation (up to 20 Gy), a similar decrease in clonogenic cells and elimination of radiation-resistant hypoxic tumor cells were observed. Potentially useful as a vascular-targeted approach for cancer therapy.



ZM-445526 [295866]^{1,3,5,10}: C20 H23 N O5

SOURCES – Angiogene Pharmaceuticals; AstraZeneca.

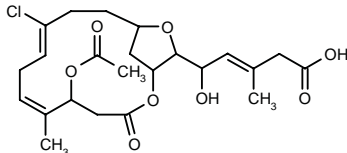
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3. Blakey, D.C. et al. *Anti-tumour of the novel vascular targeting agent ZD6126 in a human lung tumour xenograft model*. Clin Cancer Res 2000, 6(Suppl.): Abst 283.
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OTHER ONCOLYTIC DRUGS

294656

5-(5-Acetoxy-10-chloro-6-methyl-3-oxo-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-15-yl)-5-hydroxy-3-methyl-3-pentenoic acid



C23 H31 Cl O8; Mol wt: 470.9429

ACTION – Tridecanolide cytotoxic agent isolated from an ascidian *Lissoclinum* sp., shown to inhibit the proliferation of murine lymphocytic leukemia P388 cells with an IC₅₀ of 0.32 µg/ml.

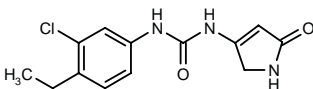
SOURCE – Sagami.

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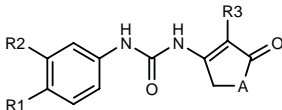
294732

N-(3-Chloro-4-ethylphenyl)-N'-(5-oxo-2,5-dihydro-1H-pyrrol-3-yl)urea



C13 H14 Cl N3 O2; Mol wt: 279.7256

ACTION – Antineoplastic agent that is active against solid tumors, in particular colon tumors. Other specifically claimed heterocyclic compounds are:



Compound	R1	R2	R3	A	Formula
294733	Cl	H	H	NH	C ₁₁ H ₁₀ ClN ₃ O ₂
294734	Et	Cl	CH ₂ N(Me) ₂	O	C ₁₆ H ₂₀ ClN ₃ O ₃
294735	Cl	H	CH ₂ N(Me) ₂	O	C ₁₄ H ₁₆ ClN ₃ O ₃

SOURCE – Novuspharma.

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ARSENIC TRIOXIDE⁺

273556



As2 O3; Mol wt: 197.8410

ACTION – Apoptosis inducer proven to produce DNA fragmentation in human promyelocytic leukemia NB4 cells *in vitro* and to cause damage or degradation of the fusion protein PML–RARα.

INDICATION – Induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to or have relapsed on retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RARα gene expression.

PRESENTATION – Ampoules (10 ml) containing injectable solution, 10 mg (1 mg/ml).

PROPRIETARY NAME – Trisenox (US).

SOURCE – Cell Therapeutics.

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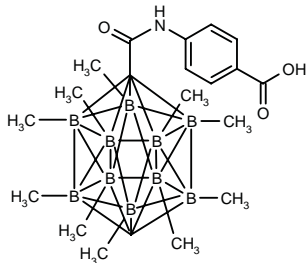
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BR-630

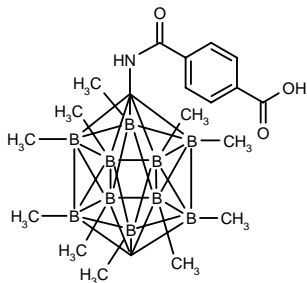
296950

4-[2,3,4,5,6,7,8,9,10,11-Decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-ylcarboxamido]benzoic acid



C20 H37 B10 N O3; Mol wt: 447.6263

ACTION – Antineoplastic agent with potent retinoid-antagonist activity in an HL-60 cell differentiation assay (IC₅₀ = 29 nM) and in retinoic acid receptor (RAR) transactivation assays (IC₅₀ = 0.16, 0.35 and 1 μM, respectively, against RARα, RARβ and RARγ). Another related compound bearing a dicarba-*closo*-dodecaborane (carborane) pharmacophore is:



BR-635 [296954]: C20 H37 B10 N O3

SOURCE – University of Tokyo, Tokyo (JP).

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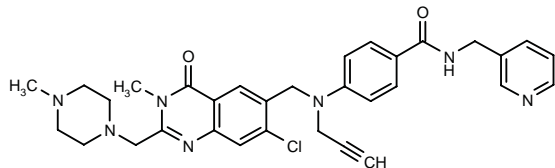
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CB-300919¹⁻³

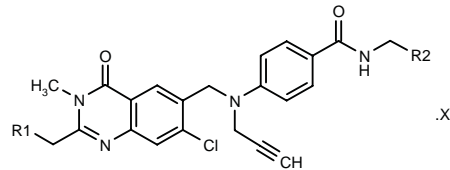
294100

4-[*N*-[7-Chloro-3-methyl-2-(4-methylpiperazin-1-ylmethyl)-4-oxo-3,4-dihydroquinazolin-6-ylmethyl]-*N*-(2-propynyl)amino]-*N*-(3-pyridylmethyl)benzamide



C32 H34 Cl N7 O2; Mol wt: 584.1206

ACTION – Antineoplastic agent, a water-soluble analogue of the folic acid analogue CB-30865, with nanomolar cytotoxicity against a panel of tumor cells including human ovarian carcinoma CH1 (IC₅₀ = 4 nM after 24-h exposure) and human colon carcinoma HT-29; it was more cytotoxic than the parent compound against human lymphoblastoid WIL2 cells, both in the presence and absence of folate metabolites (IC₅₀ = 0.45-0.49 nM vs. 2.2-2.8 nM for CB-30865). Compound did not show crossresistance with other classes of antitumor agents and produced a delayed (22 h) cell cycle arrest without phase specificity. *In vivo* in the hollow fiber model in nude mice, compound given i.p. at doses of 0.25-0.75 mg/kg/day for 3 days almost completely inhibited the growth of CH1 tumors, and it showed significant, dose-dependent activity against HT-29 xenografts (8-71% inhibition). Other quinazolines include the following:



Compound	R1	R2	X	Formula
CB-300921 [294102]¹	4-Me-1-Piz	3-Pyr	HCl	C ₃₂ H ₃₄ ClN ₇ O ₂ ·HCl
CB-300922 [294103]¹	N(Et) ₂	3-Pyr		C ₃₁ H ₃₃ ClN ₆ O ₂
CB-300930 [295744]¹⁻³	4-(CH ₂ CH ₂ -OH)-1-Piz	3-Pyr		C ₃₃ H ₃₆ ClN ₇ O ₃
CB-300929 [297489]^{1,3}	4-Me-1-Piz	1-imidazolyl-CH ₂ CH ₂		C ₃₂ H ₃₇ ClN ₈ O ₂
CB-30927 [297490]^{1,3}	4-Et-1-Piz	3-Pyr		C ₃₃ H ₃₆ ClN ₇ O ₂

SOURCE – Cancer Research Campaign Technology.

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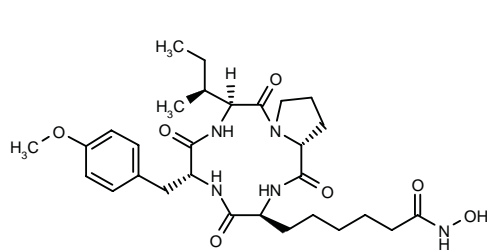
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CHAP-31

294835

Cyclo[L-isoleucyl-D-prolyl-2(*S*)-amino-8-(*N*-hydroxyamino)-8-oxooctanoyl-*O*-methyl-D-tyrosyl]



C29 H43 N5 O7; Mol wt: 573.6867

ACTION – Cytotoxic agent, an inhibitor of histone deacetylase ($IC_{50} = 3.32$ nM) with antitumor activity in mice bearing murine melanoma B16/BL6 cells.

SOURCE – Japan Energy.

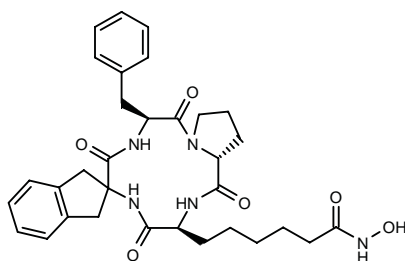
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CHAP-81

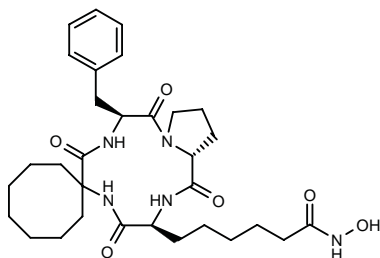
294797

(3*S*,9*S*,14*aR*)-6-(9-Benzyl-1,4,7,10-tetraoxospiro[perhydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-6,2'-indan]-3-yl)hexanehydroxamic acid

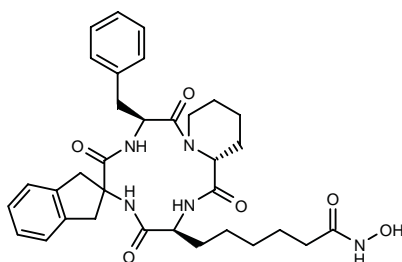


C32 H39 N5 O6; Mol wt: 589.6891

ACTION – Antineoplastic agent that acts by inhibiting histone deacetylase ($IC_{50} = 0.980$ nM against enzyme from murine melanoma B16/BL6 cells) and promoting MHC class I molecule development, as demonstrated in murine melanoma B16/BL6 cells, where it doubled the amount of developed MHC class I molecules on the surface of said cells at a concentration of 1.29 nM. Other exemplified compounds from this series of cyclic tetrapeptide derivatives include the following:



CHAP-76 [294798]: C31 H45 N5 O6



CHAP-91 [294799]: C33 H41 N5 O6

SOURCE – Japan Energy.

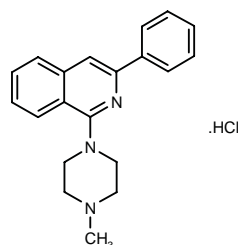
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CWJ-a-5

295393

1-(4-Methylpiperazin-1-yl)-3-phenylisoquinoline hydrochloride



C20 H21 N3 . HCl; Mol wt: 339.8678

ACTION – Antineoplastic agent, a 3-arylisoquinoline derivative with potent antitumor activity *in vivo* and *in vitro* against human tumor cell lines including non-small lung carcinoma A549, ovarian carcinoma SK-OV-3, colon carcinoma HCT-15, CNS cancer XF-498 and melanoma SK-MEL-2. Compound exhibited a good pharmacokinetic profile in rats with high oral bioavailability (64.3%).

SOURCES – Chonnam National University, Kwangju (KR); Pusan National University, Pusan (KR); Yang-Gi Chemical.

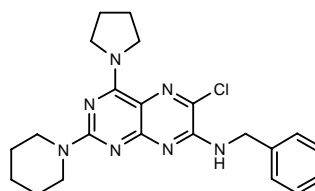
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DC-TA-46

295987

N-Benzyl-N-[6-chloro-2-(1-piperidiny)-4-(1-pyrrolidinyl)pteridin-7-yl]amine



C22 H26 Cl N7; Mol wt: 423.9494

ACTION – Antiproliferative agent, a cAMP-specific phosphodiesterase (PDE4) inhibitor (IC₅₀ = 16 nM against enzyme isolated from human solid tumors) proven to inhibit the growth of a panel of tumor cells in the low micromolar range. Compound induced arrest in the G0/G1 phase of the cell cycle followed by induction of apoptosis in human mammary carcinoma MCF-7 and human epidermoid carcinoma A-431 cells, and it inhibited phosphatidylinositol-3-kinase (PI3K) activity at growth-inhibitory concentrations in A-431 but not MCF-7 cells, indicating that inhibition of PI3K is only one of several mechanisms mediating the antiproliferative activity of the compound.

SOURCE – Universität Kaiserlautern, Kaiserslautern (DE).

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E21R

296125

Granulocyte–macrophage colony-stimulating factor analogue with a single mutation at position 21 in which glutamic acid has been substituted by arginine, expressed in Escherichia coli

ACTION – Antineoplastic agent, a recombinant analogue of granulocyte–macrophage colony-stimulating factor (GM-CSF) proven to antagonize GM-CSF-dependent cell proliferation and to induce apoptosis in cells expressing the GM-CSF receptor such as acute myeloid leukemia, juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia cells. In addition, compound inhibited both spontaneous and GM-CSF-stimulated colony formation of chronic myelomonocytic leukemia cells and prevented the dissemination of JMML cells following transplantation in a xenograft model in mice. It was well tolerated in phase I clinical trials after 10 days of treatment and is undergoing phase II studies.

SOURCES – BresaGen; British Biotech.

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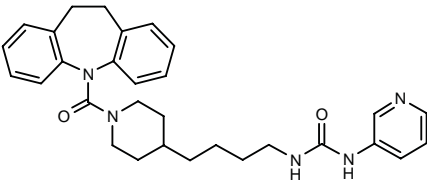
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K-22387

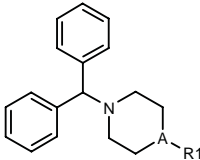
294260

N-[4-[1-(10,11-Dihydro-5-H-dibenzo[b,f]azepin-5-ylcarbonyl)piperidin-4-yl]butyl]-N'-(3-pyridyl)urea



C30 H35 N5 O2; Mol wt: 497.6395

ACTION – Antineoplastic agent that selectively inhibits NAD biosynthesis from niacinamide without blocking the niacin pathway, by inhibiting the enzyme niacinamide phosphoribosyltransferase (NAPRT). Based on the fact that malignant cells depend on niacinamide as a main or sole precursor for NAD biosynthesis, while somatic cells can also use tryptophan or niacin, providing sufficient NAD levels to guarantee survival of cells when the biosynthesis from niacinamide is inhibited, this compound is potentially useful for selective tumor therapy. K-22387 produced delayed cell death in HepG2 tumor cells at concentrations above 0.01 μM, continuing growth for up to 3 days before practically all cells underwent apoptotic cell death. The concentration necessary to kill human bone marrow cells was 10,000-fold higher when compared to most human cancer cell lines tested. Other exemplified compounds include the following:



Compound	R1	A	Formula
K-22339 [294261]	3-Pyr-CH2CH2NHCONH(CH2)4	CH	C30H38N4O
K-22132 [294263]	3-Pyr-CH2NHCONH(CH2)6NHCO	N	C31H40N6O2

SOURCE – Klinge.

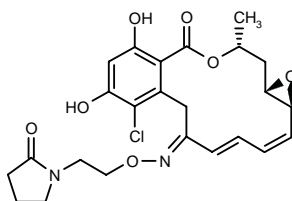
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KF-58333¹⁻⁵**282769**

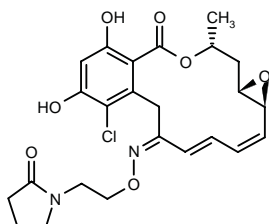
(3*R*,5*S*,6*S*,7*Z*,9*E*,11*E*)-13-Chloro-5,6-epoxy-4,16-dihydroxy-3-methyl-11-[2-(2-oxopyrrolidin-1-yl)-ethoxyimino]-3,4,5,6,11,12-hexahydro-1*H*-2-benzoxacyclotetradecin-1-one

(1*aS*,2*Z*,4*E*,6*E*,14*R*,15*aS*)-8-Chloro-9,11-dihydroxy-14-methyl-1*a*,14,15,15*a*-tetrahydro-6*H*-oxireno[*e*][2]benzoxacyclotetradecine-6,12(7*H*)-dione 6-[*O*-[2-(2-oxo-1-pyrrolidinyl)ethyl]oxime]



C24 H27 Cl N2 O7; Mol wt: 490.9373

ACTION – Antineoplastic agent, a radicicol oxime derivative proven to bind to the *N*-terminal of heat shock protein 90 (hsp90) and to deplete hsp90-associated proteins including erbB2, raf-1 and AKT from erbB2-overexpressing breast cancer KPL-4 cells. Compound was cytotoxic against human myeloid leukemia K-562 cells (IC₅₀ = 0.025 μM), arrested the cell cycle in the G1 phase and induced erythroid differentiation and apoptosis. *In vivo*, a dose of 50 mg/kg/day i.v. for 5 days strongly inhibited tumor growth in mice bearing KPL-4 xenografts and induced an increase in TUNEL-positive cells in tumor specimens. In addition, it prolonged survival of mice inoculated with K-562 cells. Other related compounds are:



Compound	Isomer	Formula
KF-55823 [267437] ^{*,1,4}	6 <i>Z</i> , <i>E</i>	C ₂₄ H ₂₇ ClN ₂ O ₇
KF-58332 [295875] ^{1,4}	6 <i>Z</i>	C ₂₄ H ₂₇ ClN ₂ O ₇

SOURCES – Kyowa Hakko; National Cancer Institute, Bethesda, MD (US).

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- Soga, S. et al. *Novel radicicol oxime hsp90 antagonist KF58333 exhibits anti-cancer activity against erb-2 over-expressing breast cancer cells of chronic myelogenous leukemia cells with bcr-abl translocation through destabilization.* Clin Cancer Res 2000, 6(Suppl.): Abst 399.

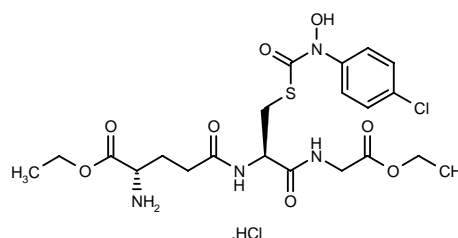
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*Identified compound **267437** (see **265114**) Drug Data Rep 1998, 020(09): 0806.

NSC-693569^{*,1,2,4-6}**272394**

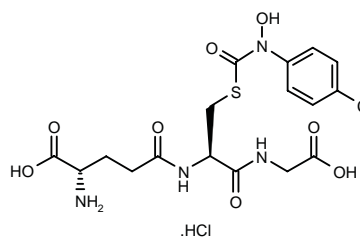
γ-L-Glutamyl-L-[*S*-[*N*-(4-chlorophenyl)-*N*-hydroxycarbamoyl]]cysteinyglycine diethyl ester hydrochloride

S-[*N*-(4-Chlorophenyl)-*N*-hydroxycarbamoyl]glutathione diethyl ester hydrochloride



C21 H29 Cl N4 O8 S . HCl; Mol wt: 569.4600

ACTION – Antineoplastic agent, a prodrug of the competitive inhibitor of the methylglyoxal-detoxifying enzyme glyoxalase I **NSC-693567** (IC₅₀ = 40 nM), proven to inhibit a variety of tumor cell lines *in vitro* including murine leukemia L1210 cells and melanoma B16 cells (IC₅₀ = 7 and 15 μM, respectively). Growth inhibition is accompanied by rapid conversion of the prodrug to the active compound inside the cell. *In vivo*, in mice bearing murine B16 melanoma and in nude mice bearing human prostate PC-3 or human colon HT-29 xenografts, the prodrug could be used to deliver the active compound into tumors at concentrations sufficient to inhibit tumor growth. I.v. administration of the prodrug exhibited antitumor efficacy comparable to doxorubicin against B16 melanoma, to cisplatin against PC-3 tumors and to vincristine against HT-29 tumors.



NSC-693567 [232441]:^{*,1-5}** C17 H21 Cl N4 O8 S . HCl

SOURCE – University of Maryland, Baltimore, MD (US).

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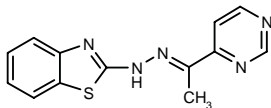
*Identified compound **272394** Drug Data Rep 1999, 021(03): 0274.

Identified compound **232441 (see **232318**) Drug Data Rep 1996, 018(05): 0471.

NSC-693632¹⁻³

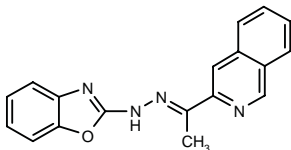
295992

1-(4-Pyrimidinyl)ethanone N-(2-benzothiazolyl)hydrazone



C13 H11 N5 S; Mol wt: 269.3309

ACTION – Antineoplastic agent with strong cytotoxic activity against human leukemia CCRF-CEM cells, Burkitt's lymphoma and human myeloid leukemia K-562 cells (IC₅₀ = 1.115, 0.140 and 0.552 μM, respectively). Compound was less active against colon carcinoma HT-29 and melanoma MEXF-276L cells (IC₅₀ = 9.5 and 3.0 μM, respectively). In an *in vivo* hollow fiber assay, it exhibited marked cytotoxic activity, and it was also found to induce apoptosis, inhibit the synthesis of RNA in a concentration-dependent manner and exert significant activity against multidrug-resistant tumor cells. Another hydrazone derivative is:



NSC-693638 [295994]¹: C18 H14 N4 O

SOURCE – Universität Innsbruck, Innsbruck (AT).

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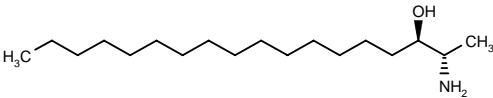
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SPISULOSINE

282749

2(S)-Aminooctadecan-3(R)-ol

Spisulosine 285
ES-285



C18 H39 N O; Mol wt: 285.5121

ACTION – Antineoplastic agent, a sphingosine-like substance isolated from the clam *Spinsula polynyma*, with selectivity for certain solid tumors including colon, gastric, pancreatic, pharyngeal and renal tumor cells, giving IC₅₀ values in the nanomolar range, and particularly good activity against hepatoma SK-HEP-1 cells (IC₅₀ = 0.562 pM); it showed generally lower activity against leukemias and lymphomas, and it was cytotoxic to normal cells only in the micromolar range. The cytotoxic activity of compound appeared to be mediated by inhibition of the Rho GTP-binding protein. Selected for clinical trials.

SOURCES – University of Illinois, Urbana-Campaign, IL (US); Pharma Mar.

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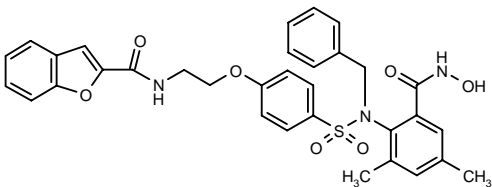
4. Jimeno, J.M. et al. *ES-285, a marine natural product with activity against solid tumors*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 314.

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WAY-170523

296174

N-[2-[4-[N-Benzyl-N-[2-(N-hydroxycarbamoyl)-4,6-dimethylphenyl]sulfamoyl]phenoxy]ethyl]-1-benzofuran-2-carboxamide



C33 H31 N3 O7 S; Mol wt: 613.6879

ACTION – Potent and selective human collagenase 3 (MMP-13) inhibitor ($IC_{50} = 17$ nM) with $> 5,800$ -, 56 - and > 500 -fold selectivity relative to MMP-1 (fibroblast collagenase), MMP-9 (gelatinase B) and TACE (TNF- α -converting enzyme), respectively. WAY-170523 is a hybrid compound incorporating selectivity features of CL-82198 and potency features of WAY-152177. Potentially useful for the treatment of diseases characterized by over-expression of MMP-13 such as breast carcinoma.

SOURCE – Wyeth-Ayerst.

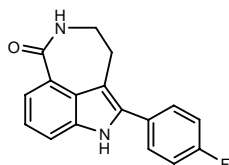
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

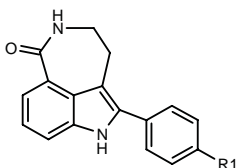
292751¹⁻⁴

2-(4-Fluorophenyl)-1,3,4,5-tetrahydro-6H-azepino-[5,4,3-cd]indol-6-one

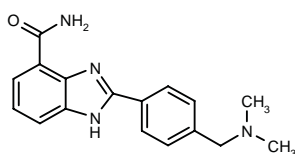


C17 H13 F N2 O; Mol wt: 280.3007

ACTION – Chemopotentiating agent, a potent inhibitor of poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase; $K_i = 4$ nM) with the ability to potentiate by 1.7-1.9-fold the *in vitro* cytotoxic activity of temozolomide and topotecan in human colon adenocarcinoma LoVo cells. Pharmacokinetic studies in mice showed high peak plasma concentrations and a long half-life, as well as excellent distribution into tumor and brain. Other related compounds include the following:



Compound	R1	Formula
292752 ¹⁻⁴	H	C ₁₇ H ₁₄ N ₂ O
295663 ^{1,3}	CH ₂ N(Me) ₂	C ₂₀ H ₂₁ N ₃ O



295664:³ C17 H18 N4 O

SOURCES – Agouron (Pfizer); Cancer Research Campaign Technology.

REFERENCES

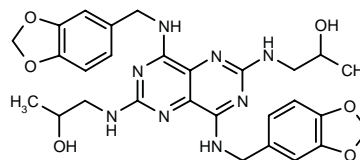
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3. Curtin, N.J. et al. *Chemopotential studies with two classes of potent (poly-ADP-ribose) polymerase (PARP) inhibitors in human lung and colon carcinoma cell lines.* Clin Cancer Res 2000, 6(Suppl.): Abst 205.
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NU-3121

295991

1-[4,8-Bis(1,3-benzodioxol-5-ylamino)-6-(2-hydroxy-propylamino)pyrimido[5,4-*d*]pyrimidin-2-ylamino]-2-propanol

1,1'-[[4,8-Bis(1,3-benzodioxolamino)pyrimido[5,4-*d*]pyrimidine-2,6-diyl]diimino]bis(2-propanol)



C28 H32 N8 O6; Mol wt: 576.6108

ACTION – Dipyridamole analogue with potent nucleoside transport-inhibitory activity ($IC_{50} = 260$ nM for inhibition of [³H]-thymidine uptake into L1210 cells). In contrast to dipyridamole, compound potentiated the *in vitro* activity of MTA (LY-231514), an antifolate antimetabolite, to a similar extent in the presence or absence of α_1 -acid glycoprotein, by preventing thymidine and hypoxanthine rescue. Compound displays a superior pharmacokinetic profile to the parent dipyridamole following i.p. administration, and was found to inhibit [³H]-thymidine incorporation into COR L23 xenografts in nude mice by 44% at a dose of 10 mg/kg i.p. Potentially useful for potentiating the activity of antifolate antimetabolites.

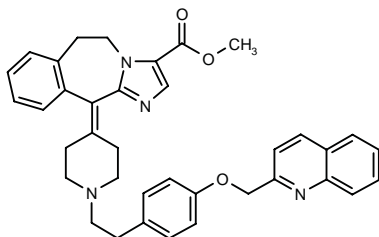
SOURCE – University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

REFERENCES

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R-101933***256166**

11-[1-[2-[4-(2-Quinolylmethoxy)phenyl]ethyl]piperidin-4-ylidene]-6,11-dihydro-5*H*-imidazo[2,1-*b*][3]benzazepine-3-carboxylic acid methyl ester



C37 H36 N4 O3; Mol wt: 584.7164

ACTION – Multidrug resistance modulator proven to restore the cytotoxic activity of anthracyclines, taxanes and vinca alkaloids in P-glycoprotein (P-gp)-overexpressing human leukemia K-562 cells, with superior potency compared to S-9788, verapamil and ciclosporin. The compound appears to act as a P-gp antagonist rather than as a substrate for P-gp. In two human tumor xenograft models (doxorubicin-resistant colon carcinoma COLO/320DM cells and doxorubicin- and paclitaxel-resistant ovarian carcinoma A2780 cells) in athymic nude mice, compound given orally was seen to restore the sensitivity of resistant tumors to both paclitaxel and doxorubicin. Phase I clinical studies showed that compound did not influence the pharmacodynamics or pharmacokinetics of paclitaxel when given as an oral formulation (200 mg b.i.d. x 5 days) to healthy volunteers. A phase I study performed in patients with advanced solid tumors demonstrated that oral compound combined with i.v. paclitaxel or docetaxel is safe and at the achieved dose levels (200 g b.i.d.p.o.) lacks a significant kinetic interaction with the anticancer drugs. The recommended phase II/III doses are: 200 g b.i.d. p.o. and 100 mg/m² docetaxel by 3-h infusion.

SOURCE – Janssen.

REFERENCES

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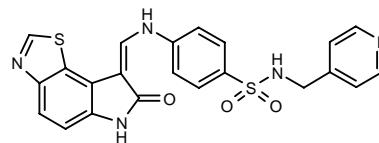
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*Identified compound **256166** Drug Data Rep 1998, 020(01): 0083.

CHEMOPROTECTIVE AGENTS**294461**

4-(7-Oxo-7,8-dihydro-6*H*-thiazolo[5,4-*e*]indol-8-ylidene-methylamino)-*N*-(4-pyridinylmethyl)benzenesulfonamide



C22 H17 N5 O3 S2; Mol wt: 463.5403

ACTION – Cyclin-dependent kinase CDK2 inhibitor potentially useful for the prevention or reduction of the severity of epithelial cytotoxic effects such as alopecia, plantar-palmar syndrome and mucositis in patients receiving chemotherapy and/or radiation therapy.

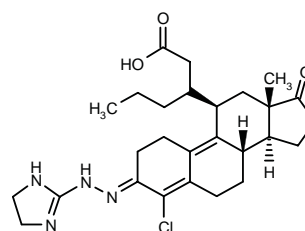
SOURCE – GlaxoSmithKline.

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METABOLIC DRUGS**TREATMENT OF BONE DISEASES****294072**

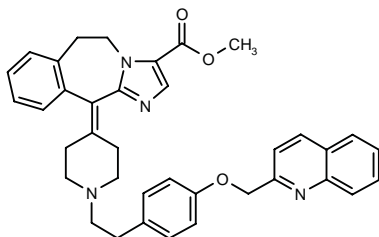
3-[4-Chloro-3-[2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazono]-17-oxoestra-4,9-dien-11β-yl]hexanoic acid



C27 H37 Cl N4 O3; Mol wt: 501.0673

R-101933***256166**

11-[1-[2-[4-(2-Quinolylmethoxy)phenyl]ethyl]piperidin-4-ylidene]-6,11-dihydro-5*H*-imidazo[2,1-*b*][3]benzazepine-3-carboxylic acid methyl ester



C37 H36 N4 O3; Mol wt: 584.7164

ACTION – Multidrug resistance modulator proven to restore the cytotoxic activity of anthracyclines, taxanes and vinca alkaloids in P-glycoprotein (P-gp)-overexpressing human leukemia K-562 cells, with superior potency compared to S-9788, verapamil and ciclosporin. The compound appears to act as a P-gp antagonist rather than as a substrate for P-gp. In two human tumor xenograft models (doxorubicin-resistant colon carcinoma COLO/320DM cells and doxorubicin- and paclitaxel-resistant ovarian carcinoma A2780 cells) in athymic nude mice, compound given orally was seen to restore the sensitivity of resistant tumors to both paclitaxel and doxorubicin. Phase I clinical studies showed that compound did not influence the pharmacodynamics or pharmacokinetics of paclitaxel when given as an oral formulation (200 mg b.i.d. x 5 days) to healthy volunteers. A phase I study performed in patients with advanced solid tumors demonstrated that oral compound combined with i.v. paclitaxel or docetaxel is safe and at the achieved dose levels (200 g b.i.d.p.o.) lacks a significant kinetic interaction with the anticancer drugs. The recommended phase II/III doses are: 200 g b.i.d. p.o. and 100 mg/m² docetaxel by 3-h infusion.

SOURCE – Janssen.

REFERENCES

1. Janssens, F.E. et al. (Janssen Pharmaceutica NV) *Fused imidazole derivs. as multidrug resistance modulators*. EP 0888352, JP 2000505477, WO 9734897.
2. Snoeck, H.J.M. (Janssen Pharmaceutica NV) *Fused imidazole derivs. for improving oral bioavailability of pharmaceutical agents*. WO 9913871.
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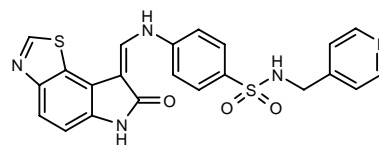
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*Identified compound **256166** Drug Data Rep 1998, 020(01): 0083.

CHEMOPROTECTIVE AGENTS**294461**

4-(7-Oxo-7,8-dihydro-6*H*-thiazolo[5,4-*e*]indol-8-ylidene-methylamino)-*N*-(4-pyridinylmethyl)benzenesulfonamide



C22 H17 N5 O3 S2; Mol wt: 463.5403

ACTION – Cyclin-dependent kinase CDK2 inhibitor potentially useful for the prevention or reduction of the severity of epithelial cytotoxic effects such as alopecia, plantar-palmar syndrome and mucositis in patients receiving chemotherapy and/or radiation therapy.

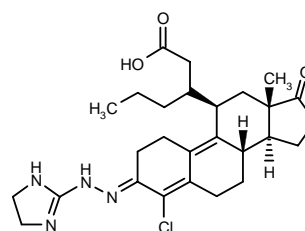
SOURCE – GlaxoSmithKline.

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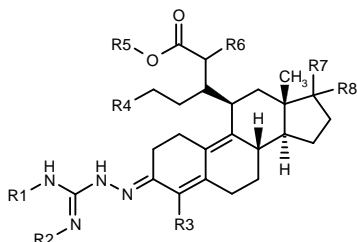
METABOLIC DRUGS**TREATMENT OF BONE DISEASES****294072**

3-[4-Chloro-3-[2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazono]-17-oxoestra-4,9-dien-11β-yl]hexanoic acid

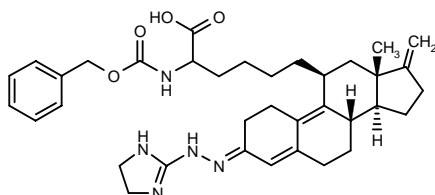


C27 H37 Cl N4 O3; Mol wt: 501.0673

ACTION – Bone resorption inhibitor with affinity for the vitronectin $\alpha_v\beta_3$ receptor ($IC_{50} = 0.017 \mu M$ for inhibition of vitronectin binding to the human vitronectin receptor). The compound is expected to be useful for the treatment of bone disorders, particularly osteoporosis, hypercalcemia, osteopenia, dental disorders, hyperparathyroidism, periarticular erosion in rheumatoid arthritis and Paget's disease, as well as cancer, inflammatory disorders, cardiovascular diseases, nephropathies and retinopathies. Other specifically claimed substituted 11β -steroids are:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
294082	-(CH ₂) ₂ -	H	Me	Et	NHCO ₂ CH ₂ Ph	-O-			C ₃₇ H ₄₉ N ₅ O ₅
294083	-(CH ₂) ₂ -	H	Me	H	NHCO ₂ CH ₂ Ph	-O-			C ₃₅ H ₄₅ N ₅ O ₅
294084	-(CH ₂) ₂ -	H	Me	H	NHCO ₂ CH ₂ Ph	OH	H		C ₃₅ H ₄₇ N ₅ O ₅
294085	H	H	H	H	H	-O-			C ₂₄ H ₃₄ N ₄ O ₃
294086	-(CH ₂) ₃ -	H	Me	H	H	-O-			C ₂₈ H ₄₀ N ₄ O ₃
294088	-(CH ₂) ₂ -	H	Me	H	H	-O-			C ₂₇ H ₃₈ N ₄ O ₃
294089	H	H	Cl	Me	H	-O-			C ₂₅ H ₃₅ ClN ₄ O ₃
294090	H	H	H	Me	H	-O-			C ₂₅ H ₃₆ N ₄ O ₃



294093: C₃₆ H₄₇ N₅ O₄

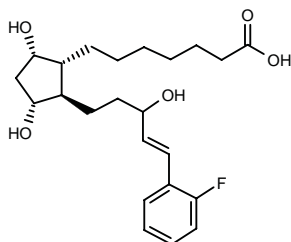
SOURCES – Aventis Pharma; Genentech.

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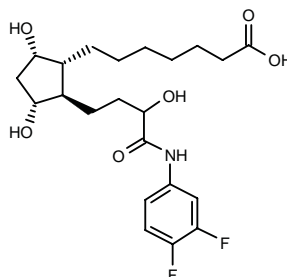
294511

17-(2-Fluorophenyl)-16,17-didehydro-13,14-dihydro-18,19,20-trinorprostaglandin F_{1α}



C₂₃ H₃₃ F O₅; Mol wt: 408.5067

ACTION – Prostaglandin F analogue able to increase bone volume, trabecular number, bone mass and/or bone formation at the endosteal surface while maintaining a normalized bone turnover rate and not increasing cortical porosity, and therefore useful for the treatment of bone disorders such as osteoporosis. It is also reported to decrease intraocular pressure and thus may be useful for the treatment of glaucoma. Another exemplified compound is:



294512: C₂₂ H₃₁ F₂ N O₆

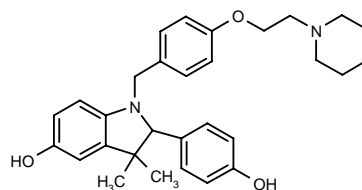
SOURCE – Procter & Gamble.

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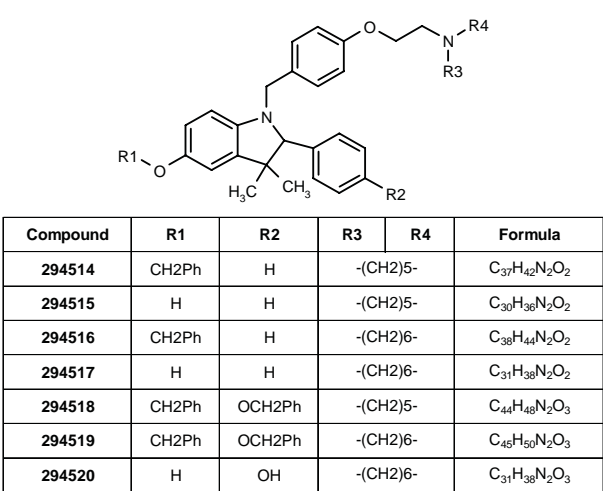
294513

2-(4-Hydroxyphenyl)-3,3-dimethyl-1-[4-[2-(1-piperidinyl)ethoxy]benzyl]-2,3-dihydro-1H-indol-5-ol



C₃₀ H₃₆ N₂ O₃; Mol wt: 472.6254

ACTION – Tissue-selective estrogen agonist/antagonist with an estrogen-like effect in bone and antiestrogenic activity in the uterus, without causing an increase in uterine weight. Its affinity for estrogen receptors was demonstrated by displacement of [³H]-17β-estradiol binding from human receptors expressed in CHO cells ($IC_{50} = 0.31 \mu M$). The compound is expected to lower cholesterol and prevent bone loss, and is potentially useful for the treatment of diseases associated with estrogen deficiency. Methods for the prevention of bone loss and for the treatment or prevention of cardiovascular diseases are specifically claimed. Other specifically claimed *N*-substituted indolines are:



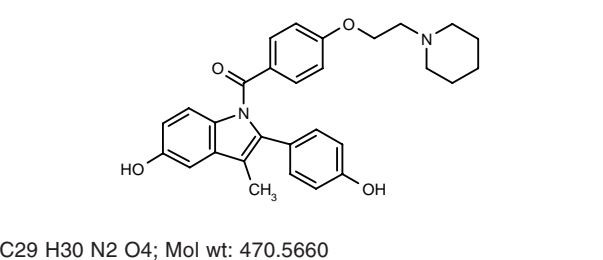
SOURCE – American Home Products.

REFERENCES

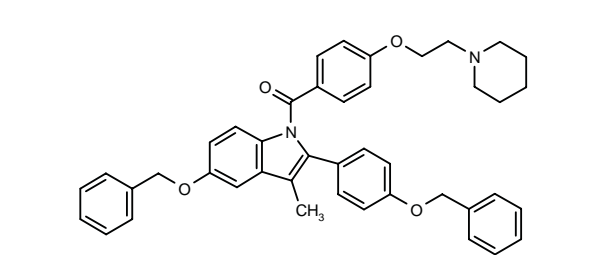
1. Ullrich, J.W. (American Home Products Corp.) *N-Substd. indolines as estrogenic agents*. WO 0051982.

294572

1-[5-Hydroxy-2-(4-hydroxyphenyl)-3-methyl-1*H*-indol-1-yl]-1-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone



ACTION – Mixed estrogen agonist/antagonist exhibiting an IC₅₀ of 0.20 μM for displacement of [³H]-17β-estradiol binding from human estrogen receptors expressed in CHO cells. This compound is tissue-selective, with an estrogen-like effect in bone and antiestrogenic activity in the uterus, and is therefore potentially useful for the treatment of diseases associated with estrogen deficiency, particularly for the treatment or prevention of bone loss and cardiovascular diseases. Another specifically claimed *N*-substituted benzoyl indole is:



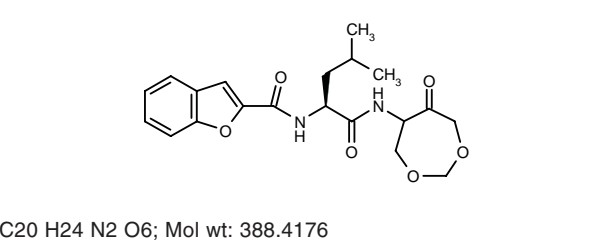
SOURCE – American Home Products.

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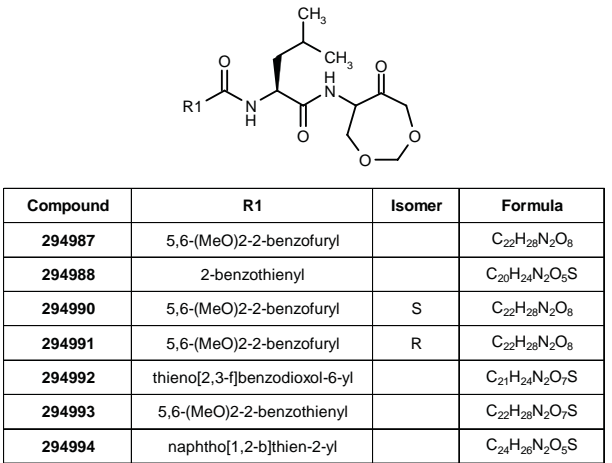
1. Koko, M.C. et al. (American Home Products Corp.) *N-Substd. benzoyl indoles as estrogenic agents*. WO 0051983.

294984

*N*²-(2-Benzofurylcarbonyl)-*N*¹-(6-oxo-1,3-dioxepan-5-yl)-L-leucinamide



ACTION – Cysteine and serine protease inhibitor, particularly active against cathepsin K, potentially useful for the treatment of disorders characterized by excessive bone or cartilage loss or matrix degradation such as osteoporosis, gingivitis, periodontitis, osteoarthritis and rheumatoid arthritis. Other specifically claimed 7-membered ring 1,3-dioxepin-5-one derivatives are:



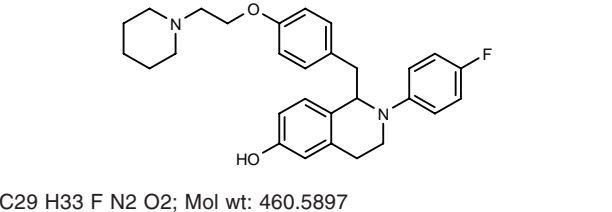
SOURCE – GlaxoSmithKline.

REFERENCES

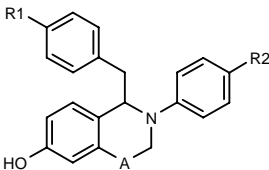
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295061

2-(4-Fluorophenyl)-1-[4-[2-(1-piperidinyl)ethoxy]benzyl]-1,2,3,4-tetrahydroisoquinolin-6-ol



ACTION – Estrogen receptor (ER) modulator with selectivity for the ER-β receptor, as demonstrated in human U2OS osteosarcoma cells stably transfected with human ER-β and ER-α receptors (IC₅₀ = 285 and 2008 nM, respectively). Potentially useful for the treatment of estrogen-related conditions such as osteoporosis and hormone-dependent cancers. Other exemplified compounds include the following:



Compound	R1	R2	A	Formula
295062	Br	H	-CH2-	C ₂₂ H ₂₀ BrNO
295063	1-Pip-CH2CH2O	F	-(CH2)2-	C ₃₀ H ₃₅ FN ₂ O ₂

SOURCES – Axys Pharmaceuticals; Signal (Celgene).

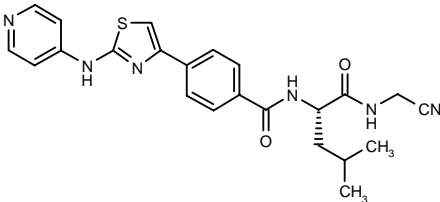
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295152

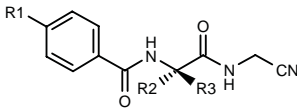
N-[1(S)-[N-(Cyanomethyl)carbamoyl]-3-methylbutyl]-4-[2-(4-pyridylamino)thiazol-4-yl]benzamide

N¹-(Cyanomethyl)-N²-[4-[2-(pyridin-4-ylamino)thiazol-4-yl]benzoyl]-L-leucinamide

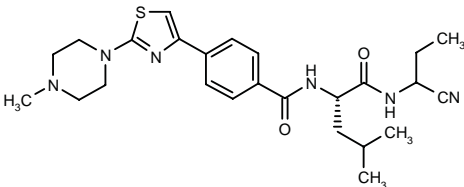


C23 H24 N6 O2 S; Mol wt: 448.5486

ACTION – An inhibitor of cysteine proteases, particularly cathepsins B, K, L and/or S, with potential for the treatment of osteoporosis, cancer, angiogenesis, rheumatoid arthritis, osteoarthritis, *Pneumocystis carinii* infection, acute pancreatitis, inflammatory airways disease and joint disorders. Other specifically claimed compounds from this series of N-cyanomethyl amide derivatives include the following:



Compound	R1	R2	R3	Formula
295153	1-(PhCH2)-3(S)-pyrrol-idinyl-N(Me)CONH	i-Bu	H	C ₂₈ H ₃₆ N ₆ O ₃
295154	2-(4-Pyr-NH)-4-thiazolyl	CH2C(Me)=CH2	H	C ₂₃ H ₂₂ N ₆ O ₂ S
295156	2-(4-Me-1-Piz)-4-thiazolyl	-(CH2)5-		C ₂₄ H ₃₀ N ₆ O ₂ S
295157	4-(4-morpholinyl-CH2)-2-thiazolyl-NH	i-Bu	H	C ₂₃ H ₃₀ N ₆ O ₃ S



295155: C25 H34 N6 O2 S

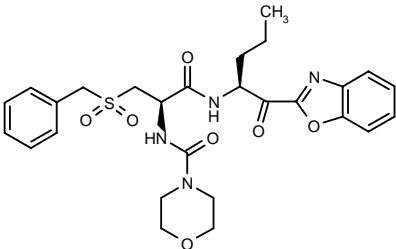
SOURCE – Axys Pharmaceuticals.

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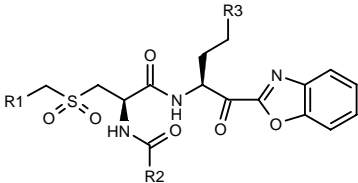
295158

N-[2-[1(S)-(2-Benzoxazolylcarbonyl)butylamino]-2-oxo-1(R)-(benzylsulfonylmethyl)ethyl]morpholine-4-carboxamide



C27 H32 N4 O7 S; Mol wt: 556.6368

ACTION – An inhibitor of cysteine proteases, particularly cathepsins B, K, L and/or S, with potential for the treatment of osteoporosis, cancer, angiogenesis, rheumatoid arthritis, osteoarthritis, *Pneumocystis carinii* infection, acute pancreatitis, inflammatory airways diseases and joint disorders. Other specifically claimed alkanoyl-substituted heterocyclic compounds include the following:



Compound	R1	R2	R3	Formula
295159	4-MeO-Ph	4-morpholinyl	Me	C ₂₈ H ₃₄ N ₄ O ₆ S
295162	3,5-(Me)2-4-isoxazolyl	4-Pyr	Et	C ₂₈ H ₃₁ N ₅ O ₇ S
295164	Ph	3-Pyr	Ph	C ₃₃ H ₃₀ N ₄ O ₆ S
295165	2-(CHF2O)-Ph	4-Pyr	Et	C ₃₀ H ₃₀ F ₂ N ₄ O ₇ S
295166	2-Me-Ph	4-morpholinyl	Ph	C ₃₃ H ₃₆ N ₄ O ₇ S
295168	2-CN-Ph	4-Pip	Ph	C ₃₄ H ₃₅ N ₅ O ₆ S

SOURCE – Axys Pharmaceuticals.

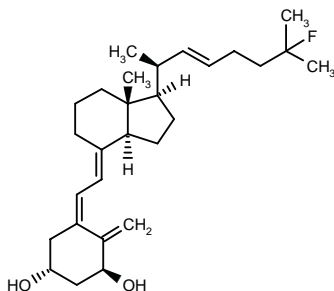
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HEP-187

294299

(*E*)-20-Epi-25-fluoro-1 α -hydroxy-22,23-didehydro-24a-homovitamin D₃



C28 H43 F O2; Mol wt: 430.6437

ACTION – 1,25-Dihydroxyvitamin D₃ analogue proven to inhibit proliferation of human osteosarcoma MG-63 cells *in vitro* (IC₅₀ = 0.42 nM vs. 1 nM for 1 α ,25(OH)₂D₃). Prolonged treatment (72 h) of MG-63 cells resulted in a concentration-dependent increase in the secretion of osteocalcin and the carboxy-terminal propeptide of procollagen type I (PICP). In an osteoporosis model in ovariectomized rats, compound given for 28 days at the daily dose of 1 μ g/kg orally induced a significant increase in vertebral bone weight and calcium content, as well as in femoral metaphysis strength; these effects were comparable to 1 α ,25(OH)₂D₃, but unlike 1 α ,25(OH)₂D₃, title compound did not induce an increase in urinary calcium excretion at pharmacologically active doses. Potentially useful for the treatment of metabolic bone diseases including osteoporosis.

SOURCE – Leo.

REFERENCES

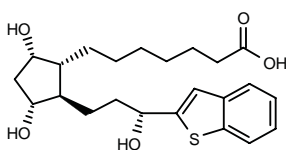
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PGE-3366466

295394

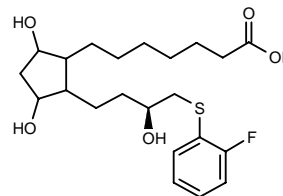
7-[(1*R*,2*R*,3*R*,5*S*)-2-[3(*R*)-(Benzo[*b*]thien-2-yl)-3-hydroxypropyl]-3,5-dihydroxycyclopentyl]heptanoic acid

15-(2-Benzothienyl)-13,14-dihydro-16,17,18,19,20-pentanorprostaglandin F_{1 α}

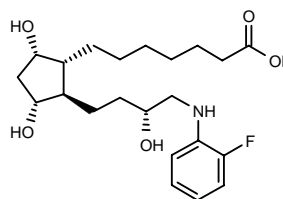


C23 H32 O5 S; Mol wt: 420.5668

ACTION – Prostaglandin analogue with anabolic activity in animal models of osteoporosis. Compound showed good water solubility and stability in both aqueous solution (pH 4 and 5) and in the solid state. It has been selected for further development as a potential drug candidate for the treatment of osteoporosis. Other related prostaglandin analogues are:



PGE-1224393 [297044]: C22 H33 F O5 S



PGE-5599419 [295395]: C22 H34 F N O5

SOURCE – Procter & Gamble.

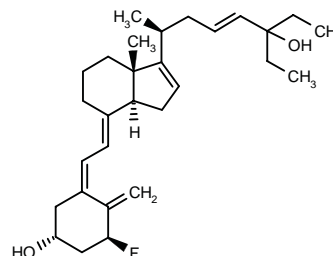
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1. deLong, M.A. et al. (The Procter & Gamble Co.) *C16 unsaturated FP-selective prostaglandins analogs*. WO 0051980.
2. Bodman, M. et al. *Preformulation characterization of several FP-series prostaglandin analogs*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abstr 3313.

RO-26-9228*

259480

(23*E*)-1 α -Fluoro-25-hydroxy-16,17,23,24-tetradehydro-26,27-bishomo-20-epivitamin D₃



C29 H43 F O2; Mol wt: 442.6547

ACTION – Vitamin D analogue proven to have beneficial effects on bone but to be devoid of adverse effects on calcium homeostasis. In a phase II clinical study in postmenopausal women receiving calcium, vitamin D and compound at a dose of 150 μ g/day for 90 days, an increase in lumbar spine bone mineral density (BMD), a significant increase in whole-body BMD and significant decreases in all bone markers studied were seen, whereas only minimal effects were seen on calcium homeostasis.

SOURCE – Roche Bioscience.

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*Identified compound **259480** (see **258701**) Drug Data Rep 1998, 020(03): 0240.

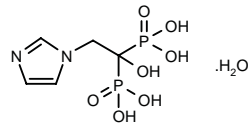
ZOLEDRONIC ACID MONOHYDRATE

Rec INNM

144428

1-Hydroxy-2-(1-imidazolyl)ethylene-1,1-diphosphonic acid monohydrate

CGP-42446⁺ (anhydrous)
ZOL-446



C5 H10 N2 O7 P2 . H2O; Mol wt: 290.1038

ACTION – Bisphosphonate that potently inhibits bone resorption and also exerts direct antitumor and anti-angiogenic effects.

INDICATION – Treatment of hypercalcemia of malignancy.

PRESENTATION – Vials containing powder for solution for infusion, 4 mg of zoledronic acid (anhydrous), corresponding to 4.264 mg zoledronic acid monohydrate.

PROPRIETARY NAME – Zometa (CA).

SOURCE – Novartis.

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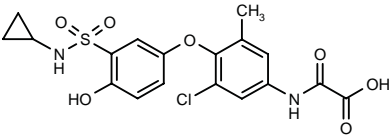
MONOGRAPH – Sorbera, L.A. et al. *Zoledronate disodium*. Drugs Fut 2000, 25(3): 0259.

*Drug Data Rep 1994, 016(07): 0656.

TREATMENT OF OBESITY
AND NUTRITIONAL DISORDERS

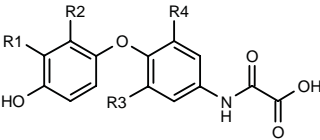
294489

N-[3-Chloro-4-[3-(N-cyclopropylsulfamoyl)-4-hydroxyphenoxy]-5-methylphenyl]oxamic acid



C18 H17 Cl N2 O7 S; Mol wt: 440.8583

ACTION – Thyroid receptor ligand, potentially useful for the treatment of obesity, hyperlipidemia, glaucoma, arrhythmia, thyroid disease, hypothyroidism and related disorders, preferably for the treatment of obesity. Other specifically claimed oxamic acids and derivatives include the following:



Compound	R1	R2	R3	R4	Formula
294490	-(CH2)3-		Me	Me	C19H19NO5
294491	cyclopropyl-CH2SO2		H	Me	C20H21NO7S
294493	cyclopentyl-CH2SO2		H	Cl	C20H19Cl2NO7S
294494	4-F-PhSO2		H	Me	C22H18FNO7S
294496	cyclobutyl-CH2SO2		H	Cl	C19H17Cl2NO7S
294498	cyclopentyl-CH2SO2		H	Me	C21H22ClNO7S
294499	4-F-PhSO2		H	Cl	C20H12Cl2FNO7S

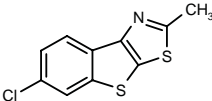
SOURCE – Pfizer.

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294521

6-Chloro-2-methylbenzo[b]thieno[3,2-d]thiazole



C10 H6 Cl N S2; Mol wt: 239.7494

ACTION – A representative compound from a series of polycyclic thiazoles with anorectic activity, potentially useful for the treatment or prophylaxis of obesity and type 2 diabetes. The compound decreased condensed milk consumption by 83% in fasted mice pretreated with 50 mg/kg p.o.

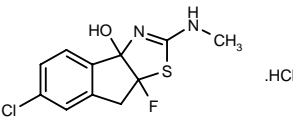
SOURCE – Aventis Pharma.

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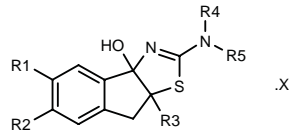
294522

6-Chloro-8a-fluoro-2-(methylamino)-8,8a-dihydro-3aH-indeno[1,2-d]thiazol-3a-ol hydrochloride



C11 H10 Cl F N2 O S . HCl; Mol wt: 309.1909

ACTION – Anorectic agent, potentially useful for the treatment or prophylaxis of obesity and type 2 diabetes. The compound decreased condensed milk consumption by 94% in fasted mice pretreated with 10 mg/kg p.o. Other exemplified polycyclic 2-aminodihydrothiazoles are:



Compound	R1	R2	R3	R4	R5	X	Formula
294523	H	Cl	H	H	H	HCl	C ₁₀ H ₉ ClN ₂ OS·HCl
294524	4-Cl-Ph	H	H	Me	Me	HBr	C ₁₈ H ₁₇ ClN ₂ OS·HBr
294525	H	Cl	F	Me	H		C ₁₁ H ₁₀ ClF ₂ N ₂ OS
294526	H	Cl	H	H	H		C ₁₀ H ₉ ClN ₂ OS

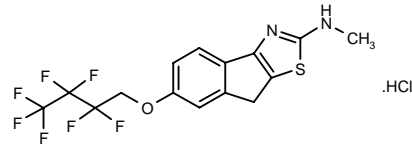
SOURCE – Aventis Pharma.

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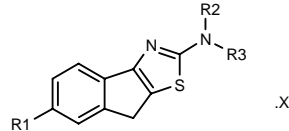
294527

6-(2,2,3,3,4,4,4-Heptafluorobutoxy)-*N*-methyl-8*H*-indeno[1,2-*d*]thiazol-2-amine hydrochloride



C15 H11 F7 N2 O S . HCl; Mol wt: 436.7778

ACTION – Anorectic agent potentially useful for the treatment or prophylaxis of obesity and type 2 diabetes. The compound decreased condensed milk consumption by 96% in fasted mice pretreated with 50 mg/kg p.o. Other exemplified polycyclic 2-aminothiazoles are:



Compound	R1	R2	R3	X	Formula
294528	CN	Me	Me	HBr	C ₁₃ H ₁₁ N ₃ S·HBr
294529	OCH2CF2CF3	Me	H	HCl	C ₁₄ H ₁₁ F ₃ N ₂ OS·HCl
294530	OCH2CF3	Me	H	HCl	C ₁₃ H ₁₁ F ₃ N ₂ OS·HCl
294531	OCH2CF3	H	H	HCl	C ₁₂ H ₉ F ₃ N ₂ OS·HCl
294532	3-Pyr	Me	H	HCl	C ₁₆ H ₁₃ N ₃ S·HCl
294533	3-Me-PhO	H	H	HCl	C ₁₇ H ₁₄ N ₂ OS·HCl

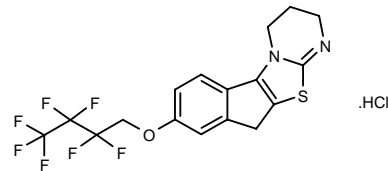
SOURCE – Aventis Pharma.

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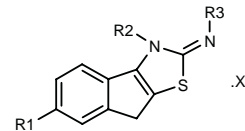
294534

8-(2,2,3,3,4,4,4-Heptafluorobutoxy)-1,2,3,6-tetrahydro-indeno[1',2':4,5]thiazolo[3,2-*a*]pyrimidine hydrochloride



C17 H13 F7 N2 O S . HCl; Mol wt: 462.8156

ACTION – Anorectic agent potentially useful for the treatment or prophylaxis of obesity and type 2 diabetes. The compound decreased condensed milk consumption by 98% in fasted mice pretreated with 50 mg/kg p.o. Other exemplified polycyclic thiazole-2-ylidene amines are:



Compound	R1	R2	R3	X	Formula
294535	4-Cl-PhO	Me	Me	HCl	C ₁₈ H ₁₅ ClN ₂ OS·HCl
294536	OCH2CF3	Me	Me	HCl	C ₁₄ H ₁₃ F ₃ N ₂ OS·HCl
294537	OCH2CF2CF2CF3	Me	Me	HCl	C ₁₆ H ₁₃ F ₇ N ₂ OS·HCl
294538	Cl	4-Cl-Ph	4-Cl-Ph		C ₂₂ H ₁₃ Cl ₃ N ₂ S

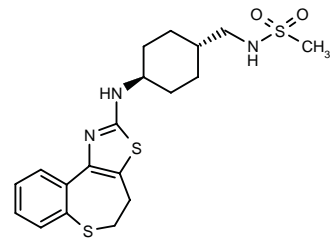
SOURCE – Aventis Pharma.

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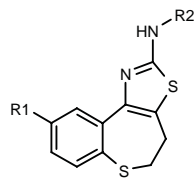
294671

trans-*N*-[4-(4,5-Dihydro[1]benzothiepine[5,4-*d*]thiazol-2-ylamino)cyclohexylmethyl]methanesulfonamide



C19 H25 N3 O2 S3; Mol wt: 423.6235

ACTION – Potent and selective neuropeptide Y (NPY) Y₅ receptor antagonist with a K_i value of 6.8 nM in a binding assay using cloned human NPY Y₅ receptors. Functional antagonism was demonstrated in the forskolin-stimulated cAMP assay in cells stably transfected with the cloned human Y₅ receptor (pK_b = 8.6). Potentially useful in the treatment of eating disorders (obesity and bulimia), sexual/reproductive disorders, depression, epilepsy, hypertension, cerebral hemorrhage, congestive heart failure and sleep disturbances. Other specifically claimed tricyclic compounds are:



Compound	R1	R2	Formula
294672	H	trans-4-(8-quinolinyl-SO2NHCH2)-cyclohexyl	C ₂₇ H ₂₈ N ₄ O ₂ S ₃
294673	Me	2-MeO-5-Me-PhSO2NH(CH2)5	C ₂₅ H ₃₁ N ₃ O ₃ S ₃
294674	H	trans-4-[i-PrN(CHO)CH2]-cyclohexyl	C ₂₂ H ₂₉ N ₃ OS ₂

SOURCE – Synaptic.

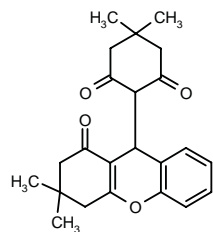
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L-152804

253960

2-(3,3-Dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)-5,5-dimethylcyclohexane-1,3-dione



C23 H26 O4; Mol wt: 366.4544

ACTION – Selective, orally available neuropeptide Y (NPY) Y₅ receptor antagonist (IC₅₀ = 27 and 31 nM, respectively, for inhibition of [¹²⁵I]-PYY binding to human and rat Y₅ receptors) with no affinity for Y₁, Y₂ and Y₄ receptors, dopamine or 5-HT receptors at up to 10 μM. Compound exhibited functional antagonism in Y₅-expressing cells, where it inhibited both NPY-induced GTPγS binding and the calcium response with respective IC₅₀ values of 148 and 170 nM. In mice, it completely abolished the increase in eating, body weight, blood insulin and total cholesterol levels induced by a specific Y₅ agonist. It also significantly inhibited bovine pancreatic peptide-induced food intake in satiated rats at does of 30 μg i.c.v. or 10 mg/kg p.o., but had no effect against NPY-induced food intake, nor did it affect food intake in *db/db* mice or Zucker fatty rats at doses of 30 or 100 mg/kg p.o. Potentially useful for the treatment of obesity and as a tool for elucidating the pathophysiological role of the Y₅ receptors in the regulation of food intake.

SOURCES – Banyu; Merck & Co.

REFERENCES

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HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

SB-251353

274552

Recombinant truncated form of the human CXC chemokine GRO-β/CXCL-2, consisting of amino acids 5-73, with a molecular weight of approximately 7500 daltons

GROβ-T

ACTION – Recombinant truncated form of the CXC chemokine GRO-β/CXCL-2, involved in neutrophil recruitment and activation, with potent antiinfective and hematopoietic activities. Compound was shown to mobilize hematopoietic stem cells in mouse transplant models and to accelerate multilineage hematopoietic reconstitution in myelosuppressed animals when given alone or in combination with granulocyte colony-stimulating factor (G-CSF). In normal mice, compound induced a rapid and dose-dependent increase in neutrophils up to 100 μg/kg; the neutrophils exhibited increased superoxide anion production, adherence and phagocytosis, as well as enhanced bactericidal activity, as demonstrated by superior *Staphylococcus aureus*-killing ability of blood obtained from SB-251353-treated animals compared to control animals. Pharmacokinetic studies in mice demonstrated that compound is mainly eliminated by glomerular filtration after i.v. bolus administration, and subsequently degraded in proximal tubular epithelial cells. Currently undergoing phase I studies as a hematopoietic agent for the treatment of chemotherapy-induced cytopenia.

SOURCE – GlaxoSmithKline.

REFERENCES

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2. Hepburn, T.W. et al. *Radiolabeled distribution study of SB-251353, a novel human CXC chemokine, in the mouse*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2657.

3. King, A.G. and Schneider, M. *Truncated GRO-beta (SB-251353) rapidly increases neutrophils with enhanced bactericidal activities in mice*. Blood 2000, 96(11, Part 1): Abst 1264.

4. King, A.G. et al. *Identification of unique truncated KC/GRObeta chemokines with potent hematopoietic and anti-infective activities*. J Immunol 2000, 164(7): 3774.

5. King, A.G. et al. *Multi-lineage effects of truncated GRObeta (SB-251353) in combination with hematopoietic growth factors in chemotherapy-induced myelosuppression models*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 212.

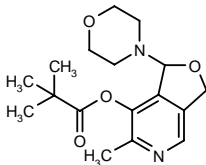
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THERAPY OF INBORN ERRORS OF METABOLISM

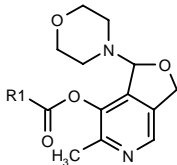
294742

Pivalic acid 6-methyl-1-(4-morpholinyl)-1,3-dihydrofuro-[3,4-*c*]pyridin-7-yl ester



C17 H24 N2 O4; Mol wt: 320.3866

ACTION – Pyridoxal prodrug shown to provide pyridoxal-5'-phosphate (PLP) levels comparable to those attained following direct administration of PLP in rats at 10 mg/kg p.o., potentially useful for the treatment of vitamin B₆ deficiency and related diseases such as hyperhomocysteinemia, as well as cardiovascular and related disorders such as hypertension, congestive heart failure, myocardial ischemia, arrhythmia and platelet aggregation, and melanoma. Other exemplified compounds from this series of 3-acylated pyridoxal analogues include the following:



Compound	R1	Formula
294744	N(Me) ₂	C ₁₅ H ₂₁ N ₃ O ₄
294745	2-AcO-Ph	C ₂₁ H ₂₂ N ₂ O ₆

SOURCE – Medigure.

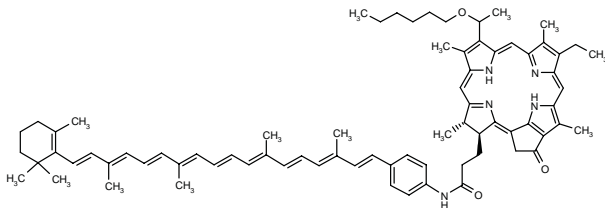
REFERENCES

1. Haque, W. (Medigure Inc.) *Pyridoxal analogues for vitamin B-6 disorders*. WO 0053606.

DIAGNOSTIC AGENTS

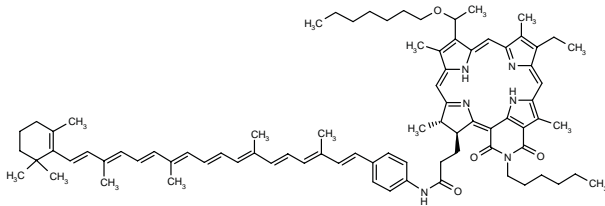
293241

7-Ethyl-12-(1-hexyloxyethyl)-3,8,13,17(*S*)-tetramethyl-18(*S*)-[2-[*N*-[4-[3-3,7,12,16-tetramethyl-18-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1(*E*),3(*E*),5(*E*),7(*E*),9(*E*),11(*E*),13(*E*),15(*E*),17(*E*)-octadecanonaen-1-yl]-phenyl]carbamoyl]ethyl]-2¹,2²,17,18-tetrahydrocyclopenta[*a*,*f*]porphyrin-2¹-one



C76 H93 N5 O3; Mol wt: 1124.6030

ACTION – Agent for the diagnosis of tumors by fluorescence spectroscopy, a representative compound from a series of carotene conjugates of porphyrins, chlorins and bacteriochlorins. These compounds, while being ineffective as antitumor agents, exhibit higher uptake into tumors versus skin compared to the base compounds and are thus devoid of the photosensitizing side effects of said base compounds. Another exemplified compound is:



293495: C83 H106 N6 O4

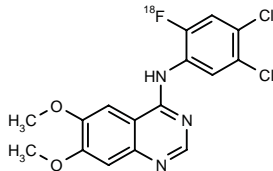
SOURCE – Health Research.

REFERENCES

1. Pandey, R.K. et al. (Health Research, Inc.) *Carotene analogs of porphyrins, chlorins and bacteriochlorins as therapeutic and diagnostic agents*. US 6103751.

294846

N-(6,7-Dimethoxyquinazolin-4-yl)-*N*-(4,5-dichloro-2-[¹⁸F]fluorophenyl)amine

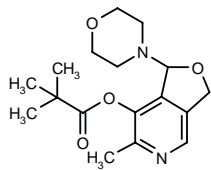


C16 H12 Cl2 F N3 O2; Mol wt: 367.1958

THERAPY OF INBORN ERRORS OF METABOLISM

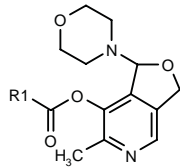
294742

Pivalic acid 6-methyl-1-(4-morpholinyl)-1,3-dihydrofuro-[3,4-*c*]pyridin-7-yl ester



C17 H24 N2 O4; Mol wt: 320.3866

ACTION – Pyridoxal prodrug shown to provide pyridoxal-5'-phosphate (PLP) levels comparable to those attained following direct administration of PLP in rats at 10 mg/kg p.o., potentially useful for the treatment of vitamin B₆ deficiency and related diseases such as hyperhomocysteinemia, as well as cardiovascular and related disorders such as hypertension, congestive heart failure, myocardial ischemia, arrhythmia and platelet aggregation, and melanoma. Other exemplified compounds from this series of 3-acylated pyridoxal analogues include the following:



Compound	R1	Formula
294744	N(Me) ₂	C ₁₅ H ₂₁ N ₃ O ₄
294745	2-AcO-Ph	C ₂₁ H ₂₂ N ₂ O ₆

SOURCE – Medigure.

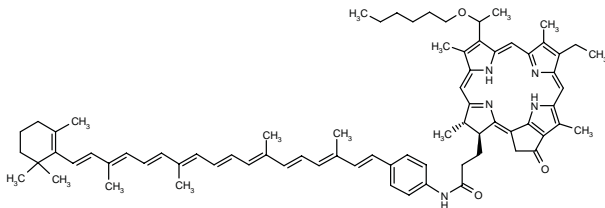
REFERENCES

1. Haque, W. (Medigure Inc.) *Pyridoxal analogues for vitamin B-6 disorders*. WO 0053606.

DIAGNOSTIC AGENTS

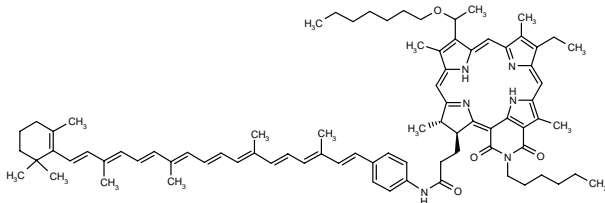
293241

7-Ethyl-12-(1-hexyloxyethyl)-3,8,13,17(*S*)-tetramethyl-18(*S*)-[2-[*N*-[4-[3-3,7,12,16-tetramethyl-18-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1(*E*),3(*E*),5(*E*),7(*E*),9(*E*),11(*E*),13(*E*),15(*E*),17(*E*)-octadecanonaen-1-yl]-phenyl]carbamoyl]ethyl]-2¹,2²,17,18-tetrahydrocyclopenta[*a*,*f*]porphyrin-2¹-one



C76 H93 N5 O3; Mol wt: 1124.6030

ACTION – Agent for the diagnosis of tumors by fluorescence spectroscopy, a representative compound from a series of carotene conjugates of porphyrins, chlorins and bacteriochlorins. These compounds, while being ineffective as antitumor agents, exhibit higher uptake into tumors versus skin compared to the base compounds and are thus devoid of the photosensitizing side effects of said base compounds. Another exemplified compound is:



293495: C83 H106 N6 O4

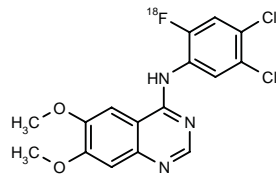
SOURCE – Health Research.

REFERENCES

1. Pandey, R.K. et al. (Health Research, Inc.) *Carotene analogs of porphyrins, chlorins and bacteriochlorins as therapeutic and diagnostic agents*. US 6103751.

294846

N-(6,7-Dimethoxyquinazolin-4-yl)-*N*-(4,5-dichloro-2-[¹⁸F]fluorophenyl)amine



C16 H12 Cl2 F N3 O2; Mol wt: 367.1958

ACTION – Radiolabeled epidermal growth factor (EGF) receptor kinase inhibitor ($IC_{50} = 0.22 \pm 0.18$ nM for inhibition of EGF receptor autophosphorylation), useful as a biomarker for positron emission tomography (PET) in cancer diagnosis, staging and therapy protocol selection.

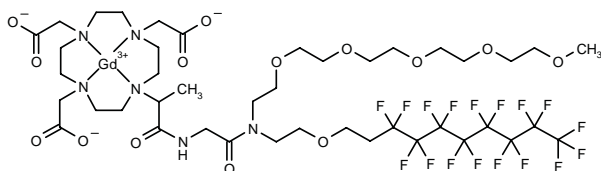
SOURCE – Hadasit Medical Research Services and Development.

REFERENCES

1. Mishani, E. et al. (Hadasit Medical Research Services and Development Ltd.) *Epidermal growth factor receptor binding cpds. for positron emission tomography*. US 6126917, WO 0072849.

295171

[10-[6-[2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyloxy)ethyl]-1-methyl-2-(oxo- κ O)-5-oxo-9,12,15,18,21-pentaoxa-3,6-diazadocos-1-yl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)- κ N¹, κ N⁴, κ N⁷, κ N¹⁰, κ O¹, κ O⁴, κ O⁷]gadolinium



C42 H60 F17 Gd N6 O14; Mol wt: 1353.1800

ACTION – A representative compound from a series of macrocyclic perfluoroalkylamide metal complexes useful as contrast agents for nuclear magnetic resonance (NMR) and X-ray imaging, as well as in radiotherapy. These compounds possess the advantage over extracellular contrast media such as Dy-DTPA that they are dispersed exclusively in the vascular space. They are also reported to be suited for MRT lymphography.

SOURCE – Schering AG.

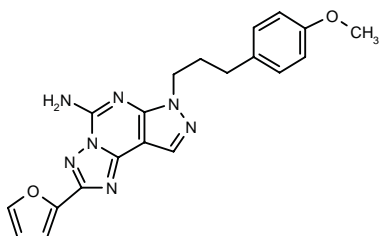
REFERENCES

1. Platzek, J. et al. (Schering AG) *Perfluoroalkylamide, the production thereof and the use thereof in diagnostics*. WO 0056723.

SCH-442416

297103

2-(2-Furyl)-7-[3-(4-methoxyphenyl)propyl]-7H-pyrazolo-[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine-5-amine



C20 H19 N7 O2; Mol wt: 389.4171

ACTION – Potent and selective adenosine A_{2A} receptor ligand ($K_i = 0.048$ and 0.50 nM for human and rat receptors, respectively) with low affinity for A₁ receptors ($K_i = 1.1$ μ M), A_{2B} and A₃ receptors ($K_i > 10$ μ M). The [¹¹C]-labeled form of the compound showed good distribution in both peripheral and central rat tissues, particularly in adrenal glands, kidneys, lungs, liver and striatum. Radiolabeled compound showed a good signal-to-noise ratio between 5 and 15 min after injection and was metabolized slowly. Potentially useful for *in vivo* imaging of A_{2A} receptors using positron emission tomography (PET).

SOURCE – Schering-Plough.

REFERENCES

1. Todde, S. et al. *Design, radiosynthesis, and biodistribution of a new potent and selective ligand for in vivo imaging of the adenosine A_{2A} receptor system using positron emission tomography*. J Med Chem 2000, 43(23): 4359.

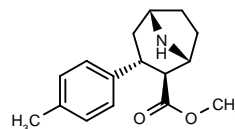
PHARMACOLOGICAL TOOLS

RTI-362

296298

3 α -(4-Methylphenyl)nortropane-2 β -carboxylic acid methyl ester

3*endo*-(4-Methylphenyl)-8-azabicyclo[3.2.1]octane-2*exo*-carboxylic acid methyl ester



C16 H21 N O2; Mol wt: 259.3469

ACTION – Potent and selective 3-phenyltropane-based inhibitor of the noradrenaline transporter ($IC_{50} = 9.0$ nM against [³H]-nisoxetine binding) relative to the dopamine ($IC_{50} = 33.6$ nM against [³H]-Win-35428) and 5-HT ($IC_{50} = 500$ nM against [³H]-paroxetine) transporters.

SOURCES – Research Triangle Institute; National Institute on Drug Abuse, Bethesda, MD (US).

REFERENCES

1. Blough, B.E. et al. *3 α -(4-Substituted phenyl) nortropane-2 β -carboxylic acid methyl esters show selective binding at the norepinephrine transporter*. Bioorg Med Chem Lett 2000, 10(21): 2445.

ACTION – Radiolabeled epidermal growth factor (EGF) receptor kinase inhibitor ($IC_{50} = 0.22 \pm 0.18$ nM for inhibition of EGF receptor autophosphorylation), useful as a biomarker for positron emission tomography (PET) in cancer diagnosis, staging and therapy protocol selection.

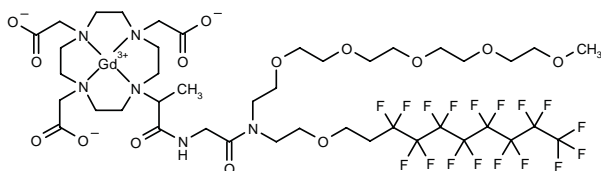
SOURCE – Hadasit Medical Research Services and Development.

REFERENCES

1. Mishani, E. et al. (Hadasit Medical Research Services and Development Ltd.) *Epidermal growth factor receptor binding cpds. for positron emission tomography*. US 6126917, WO 0072849.

295171

[10-[6-[2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyloxy)ethyl]-1-methyl-2-(oxo- κ O)-5-oxo-9,12,15,18,21-pentaoxa-3,6-diazadocos-1-yl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)- κ N¹, κ N⁴, κ N⁷, κ N¹⁰, κ O¹, κ O⁴, κ O⁷]gadolinium



C42 H60 F17 Gd N6 O14; Mol wt: 1353.1800

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SOURCE – Schering AG.

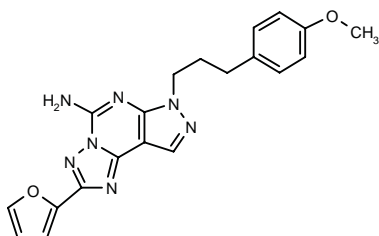
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SCH-442416

297103

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SOURCE – Schering-Plough.

REFERENCES

1. Todde, S. et al. *Design, radiosynthesis, and biodistribution of a new potent and selective ligand for in vivo imaging of the adenosine A_{2A} receptor system using positron emission tomography*. J Med Chem 2000, 43(23): 4359.

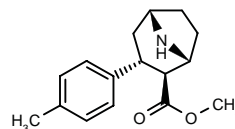
PHARMACOLOGICAL TOOLS

RTI-362

296298

3 α -(4-Methylphenyl)nortropane-2 β -carboxylic acid methyl ester

3*endo*-(4-Methylphenyl)-8-azabicyclo[3.2.1]octane-2*exo*-carboxylic acid methyl ester



C16 H21 N O2; Mol wt: 259.3469

ACTION – Potent and selective 3-phenyltropane-based inhibitor of the noradrenaline transporter ($IC_{50} = 9.0$ nM against [³H]-nisoxetine binding) relative to the dopamine ($IC_{50} = 33.6$ nM against [³H]-Win-35428) and 5-HT ($IC_{50} = 500$ nM against [³H]-paroxetine) transporters.

SOURCES – Research Triangle Institute; National Institute on Drug Abuse, Bethesda, MD (US).

REFERENCES

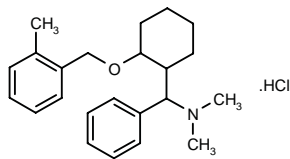
1. Blough, B.E. et al. *3 α -(4-Substituted phenyl) nortropane-2 β -carboxylic acid methyl esters show selective binding at the norepinephrine transporter*. Bioorg Med Chem Lett 2000, 10(21): 2445.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

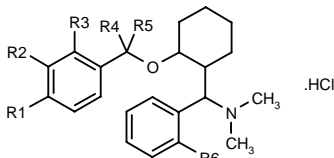
295338

N,N-Dimethyl-1-[2-(2-methylbenzyloxy)cyclohexyl]-1-phenyl-methanamine hydrochloride



C₂₃ H₃₁ N O . HCl; Mol wt: 373.9648

ACTION – Analgesic agent with high affinity for the sodium channel binding site 2 (BTX binding site; 99% inhibition of [³H]-batrachotoxin A20 α -benzoate binding in rat cortex at 10 μ M) and benzothiazepine site of L-type calcium channels (82% inhibition of [³H]-*cis*-(+)-diltiazem binding in rat cortex at 10 μ M). *In vivo*, compound gave 85% inhibition of phenylbenzoquinone-induced writhing in mice at 10 mg/kg i.v. Also reported to be useful as a local anesthetic and as an antiarrhythmic, antiemetic and nootropic agent, as well as for the treatment of cardiovascular disorders, urinary incontinence, diarrhea, pruritus, inflammation and alcohol and drug dependence. Other specifically claimed compounds from this series of 3-amino-3-arylpropan-1-ol derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
295340	CF ₃	H	H	-O-	H	H	C ₂₃ H ₂₆ F ₃ NO ₂ .HCl
295341	OMe	H	H	-O-	H	H	C ₂₃ H ₂₉ NO ₃ .HCl
295342	H	H	Cl	H	H	Cl	C ₂₂ H ₂₇ Cl ₂ NO.HCl
295343	H	F	H	H	H	H	C ₂₂ H ₂₈ FNO.HCl
295344	F	H	H	H	H	H	C ₂₂ H ₂₈ FNO.HCl

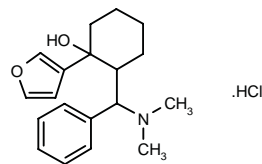
SOURCE – Grünenthal.

REFERENCES

1. Sundermann, B. et al. (Grünenthal GmbH) *3-Amino-3-arylpropan-1-ol-derivates, their preparation and use*. EP 1043306, JP 2000327643.

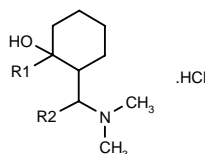
295345

2-[1-(Dimethylamino)-1-phenylmethyl]-1-(3-furyl)cyclohexanol hydrochloride



C₁₉ H₂₅ N O₂ . HCl; Mol wt: 335.8724

ACTION – Analgesic agent with affinity for the sodium channel binding site 2 (BTX binding site; 70% inhibition of [³H]-batrachotoxin A20 α -benzoate binding in rat cortex at 10 μ M) and the benzothiazepine and phenylalkylamine binding sites on L-type calcium channels (54 and 72% inhibition, respectively, of [³H]-*cis*-(+)-diltiazem and *N*-methyl-[³H]-verapamil binding in rat cortex at 10 μ M), also reported to inhibit synaptosomal noradrenaline reuptake (57% inhibition at 1 μ M in rat brain synaptosomes). *In vivo*, compound gave 100% inhibition of phenylbenzoquinone-induced writhing in mice at 10 mg/kg i.v. Also reported to be useful as a local anesthetic and as an antiarrhythmic, antiemetic and nootropic agent, as well as for the treatment of cardiovascular disorders, urinary incontinence, diarrhea, pruritus, inflammation and alcohol and drug dependence. Other specifically claimed compounds from this series of 3-amino-3-arylpropan-1-ol derivatives include the following:



Compound	R1	R2	Formula
295346	4-MeO-Ph	Ph	C ₂₂ H ₂₉ NO ₂ .HCl
295347	3-MeO-PhCH ₂	Ph	C ₂₃ H ₃₁ NO ₂ .HCl
295348	Bu	Ph	C ₁₉ H ₃₁ NO.HCl
295349	4-Cl-PhCH ₂	Ph	C ₂₂ H ₂₈ ClNO.HCl
295350	4-F-PhCH ₂	Ph	C ₂₂ H ₂₈ FNO.HCl
295351	4-t-Bu-PhCH ₂	Ph	C ₂₈ H ₃₇ NO.HCl
295352	3-Cl-PhCH ₂	Ph	C ₂₂ H ₂₈ ClNO.HCl
295353	3-CF ₃ -PhCH ₂	Ph	C ₂₃ H ₂₈ F ₃ NO.HCl
295354	CH ₂ Ph	3-Cl-Ph	C ₂₂ H ₂₈ ClNO.HCl
295355	4-MeO-PhCH ₂	Ph	C ₂₃ H ₃₁ NO ₂ .HCl
295356	4-t-Bu-PhCH ₂	2-thienyl	C ₂₄ H ₃₅ NOS.HCl

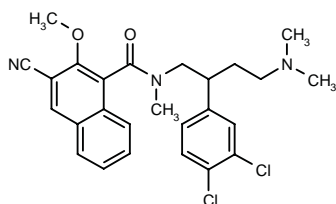
SOURCE – Grünenthal.

REFERENCES

1. Sundermann, B. et al. (Grünenthal GmbH) *3-Amino-3-arylpropan-1-ol-derivates, their preparation and their use*. EP 1043307, JP 2000327642.

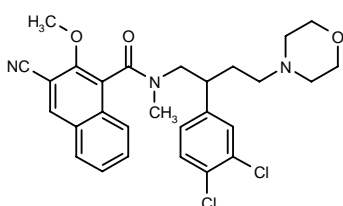
295456

3-Cyano-*N*-[2-(3,4-dichlorophenyl)-4-(dimethylamino)-butyl]-2-methoxy-*N*-methylnaphthalene-1-carboxamide



C₂₆ H₂₇ Cl₂ N₃ O₂; Mol wt: 484.4243

ACTION – Tachykinin NK₁ receptor antagonist giving a pK_b value of 8.7 in an *in vitro* functional assay in rabbit pulmonary artery. Potentially useful for the treatment of rheumatoid arthritis, Alzheimer's disease, cancer, schizophrenia, edema, allergic rhinitis, inflammation, pain, gastrointestinal hypermotility, gastroesophageal reflux, anxiety, emesis, Huntington's disease, psychoses, hypertension, migraine and urticaria. Another exemplified compound from this series of *N*-(2-phenyl-4-aminobutyl)-1-naphthamides is:



295457: C₂₈ H₂₉ Cl₂ N₃ O₃

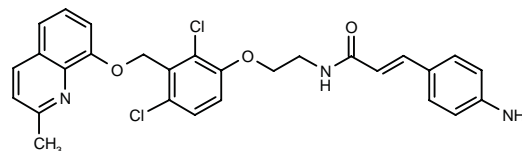
SOURCE – AstraZeneca.

REFERENCES

1. Bernstein, P.R. (AstraZeneca AB) *N*-(2-Phenyl-4-amino-butyl)-1-naphthamides as neurokinin-1 receptor antagonists. WO 0059873.

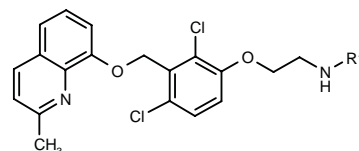
295941

3-(4-Aminophenyl)-*N*-[2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)phenoxy]ethyl]-2(*E*)-propenamide



C₂₈ H₂₅ Cl₂ N₃ O₃; Mol wt: 522.4295

ACTION – Bradykinin B₂ receptor antagonist (K_i = 20 nM against [³H]-bradykinin binding to guinea pig ileum membrane preparations), reported to exhibit improved water solubility. This compound is expected to be useful in the treatment or prevention of diseases mediated by bradykinin and its analogues such as allergy, inflammation, autoimmune diseases, shock and pain. A representative compound from a series of aminoalkyl and acyl-aminoalkyl ethers, wherein the following are also included:



Compound	R1	Formula
295942	COCH=CHPh	C ₂₈ H ₂₄ Cl ₂ N ₂ O ₃
295944	4-MeO-PhCH=CHCO	C ₂₉ H ₂₆ Cl ₂ N ₂ O ₄
296364	H	C ₁₉ H ₁₈ Cl ₂ N ₂ O ₂

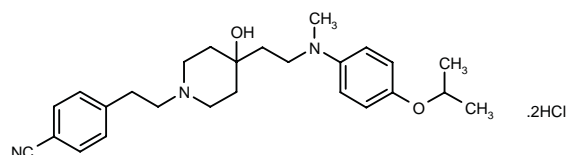
SOURCE – Aventis Pharma.

REFERENCES

1. Heitsch, H. et al. (Aventis Pharma AG) *Aminoalkyl and acylaminoalkyl ethers, process for their preparation, and their use as bradykinin receptor antagonists*. DE 19609827, EP 0795547, US 6140341.

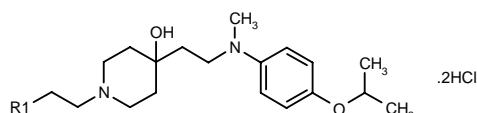
296073

4-[2-[4-Hydroxy-4-[2-[*N*-(4-isopropoxyphenyl)-*N*-methyl-amino]ethyl]piperidin-1-yl]ethyl]benzonitrile dihydrochloride



C₂₆ H₃₅ N₃ O₂ . 2HCl; Mol wt: 494.5033

ACTION – Selective, long-acting sodium channel blocker for the treatment of pain, particularly neuropathic pain, reported to exhibit few side effects. *In vitro*, compound inhibited [³H]-batrachotoxin A20 α -benzoate binding in rat brain synaptosomes with an IC₅₀ value of 0.61 μ M and veratrine-induced contractions of isolated rat cardiac muscle with an IC₅₀ value of 1.56 μ M. It exhibited antinociceptive activity in the formalin test in rats at 10 mg/kg p.o. No mortality or signs of toxicity were observed following administration of 10 mg/kg/day p.o. for 2 weeks. Other exemplified compounds from this series of 4-hydroxypiperidine derivatives include the following:



Compound	R1	Formula
296074	Ph	C ₂₅ H ₃₅ N ₂ O ₂ ·2HCl
296075	4-F-Ph	C ₂₅ H ₃₅ FN ₂ O ₂ ·2HCl
296076	2-thienyl	C ₂₃ H ₃₄ N ₂ O ₂ S·2HCl
296678	2-CF ₃ -Ph	C ₂₆ H ₃₅ F ₃ N ₂ O ₂ ·2HCl

SOURCE – Mochida.

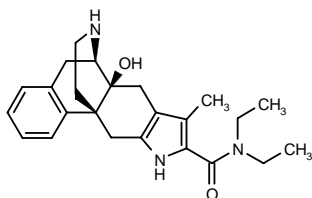
REFERENCES

1. Yamamoto, I. et al. (Mochida Pharmaceutical Co., Ltd.) *Remedies for neuropathic pain*. WO 0061558.

296258

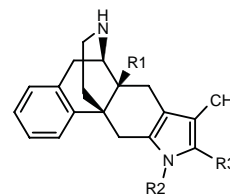
(6*R*,6*aS*,11*aR*)-*N,N*-Diethyl-6*a*-hydroxy-8-methyl-6,6*a*,7,10,11,11*a*-hexahydro-5*H*-6,11*a*-(iminoethano)-phenanthro[3,2-*b*]pyrrole-9-carboxamide

N',N'-Diethyl-14-hydroxy-4'-methylpyrrolo[2',3':6,7]-morphinan-5'-carboxamide



C₂₄ H₃₁ N₃ O₂; Mol wt: 393.5279

ACTION – Selective delta opioid receptor agonist, potentially useful as an analgesic, immunosuppressant to prevent rejection of organ transplants and skin grafts, antiallergic and antiinflammatory agent, neuroprotectant, to decrease gastric secretion and for the treatment of drug and alcohol abuse, diarrhea, cardiovascular and respiratory diseases, cough, mental illness, epileptic seizures and other neurological disorders. Compound exhibits good metabolic stability when incubated in human microsomes. Other exemplified compounds from this series of heterocycle-condensed morphinoid derivatives include the following:



Compound	R1	R2	R3	Formula
296259	OH	H	CON(i-Pr) ₂	C ₂₆ H ₃₅ N ₃ O ₂
296260	H	H	CON(i-Pr)CH ₂ Ph	C ₃₀ H ₃₅ N ₃ O
296261	OH	H	CON(Et)CH ₂ Ph	C ₂₉ H ₃₃ N ₃ O ₂
296262	OH	H	1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₈ H ₃₁ N ₃ O
296264	OH	H	i-BuCO	C ₂₄ H ₃₀ N ₂ O ₂
296265	OH	H	CON(Et)Ph	C ₂₈ H ₃₁ N ₃ O ₂
296267	H	H	CON(Et)Ph	C ₂₈ H ₃₁ N ₃ O
296268	OH	Me	CON(i-Pr)CH ₂ Ph	C ₃₁ H ₃₇ N ₃ O ₂
296272	H	Me	CON(Et)CH ₂ Ph	C ₃₀ H ₃₅ N ₃ O

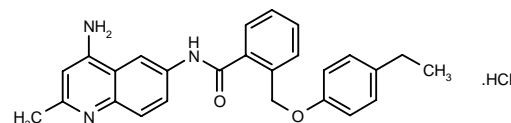
SOURCE – GlaxoSmithKline.

REFERENCES

1. Clarke, S.E. et al. (SmithKline Beecham plc; SmithKline Beecham SpA) *Morphinoid cpds*. WO 0063210.

297035

N-(4-Amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxy-methyl)benzamide hydrochloride



C₂₆ H₂₅ N₃ O₂ · HCl; Mol wt: 447.9634

ACTION – Analgesic agent, a small-molecule orphanin FQ (OFQ, nociceptin, ORL1) receptor antagonist proven to block nociceptin-induced inhibition of forskolin-stimulated cAMP accumulation in HeLa cells and to act as a highly selective OFQ receptor antagonist (K_i = 8.2 nM) relative to other opioid receptors (mu, kappa and delta K_i > 100 nM). Orally administered compound decreased nociceptin-induced allodynia in mice, delayed the avoidance response to heat in the mouse hot-plate test and decreased the formalin-induced paw-licking response in rats; its effects were not blocked by naloxone. Clinical trials are in progress.

SOURCE – Japan Tobacco.

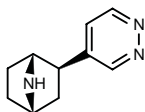
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2. Shinkai, H. et al. *4-Aminoquinolones: Novel nociceptin antagonists with analgesics activity*. J Med Chem 2000, 43(24): 4667.

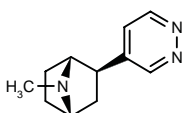
297908

exo-2-(4-Pyridazinyl)-7-azabicyclo[2.2.1]heptane



C10 H13 N3; Mol wt: 175.2337

ACTION – Potent and highly effective acetylcholine nicotinic receptor agonist, especially active on the $\alpha 4\beta 2$ subtype, potentially useful as a nonopioid analgesic. Another epibatidine analogue is:



297911: C11 H15 N3

SOURCE – Bayer.

REFERENCES

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ANTIMIGRAINE DRUGS

ALMOTRIPTAN⁺

Prop INN

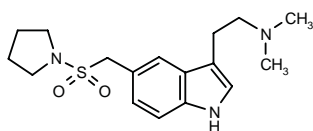
208489

3-[2-(Dimethylamino)ethyl]-5-(pyrrolidin-1-ylsulfonylmethyl)-1*H*-indole

LAS-31416

PNU-180638

AxertTM (US)



C17 H25 N3 O2 S; Mol wt: 335.4720

ACTION – Triptan antimigraine agent, a selective 5-HT_{1B/1D} receptor agonist.

INDICATION – Acute treatment of the headache phase of migraine with or without aura.

PRESENTATION – Tablets, 12.5 mg almotriptan as hydrogen D,L-malate salt.

PROPRIETARY NAME – *Almogran* (DK, ES, FI, GB).

SOURCES – Almirall Prodesfarma; marketed in Scandinavia and the U.K. by Lundbeck.

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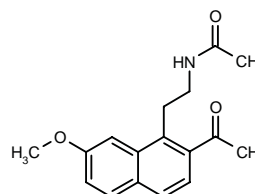
*Drug Data Rep 1997, 019(08): 0688.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

295940

N-[2-(2-Acetyl-7-methoxynaphthalen-1-yl)ethyl]acetamide



C17 H19 N O3; Mol wt: 285.3411

ACTION – Melatonergic agent with improved hypnotic and sedative effects compared to melatonin, as demonstrated *in vivo* in chicks. Potentially useful for the treatment of diseases associated with disorders of melatonin activity, and particularly for inducing sedation.

SOURCES – Besins-Iscovesco; CEMAF.

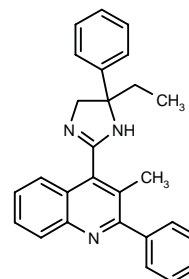
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ANXIOLYTICS

295379

4-(5-Ethyl-5-phenyl-4,5-dihydro-1H-imidazol-2-yl)-3-methyl-2-phenylquinoline



C27 H25 N3; Mol wt: 391.5155

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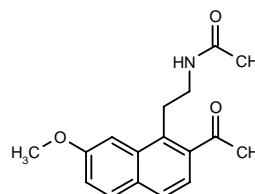
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

295940

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C17 H19 N O3; Mol wt: 285.3411

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SOURCES – Besins-Iscovesco; CEMAF.

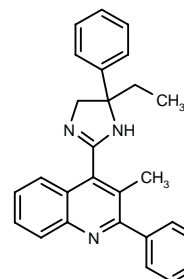
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ANXIOLYTICS

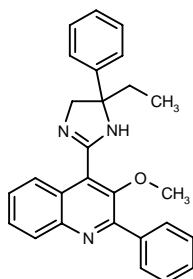
295379

4-(5-Ethyl-5-phenyl-4,5-dihydro-1H-imidazol-2-yl)-3-methyl-2-phenylquinoline



C27 H25 N3; Mol wt: 391.5155

ACTION – Neurokinin NK₃ (IC₅₀ = 0.3 nM for human NK₃ receptors cloned in CHO cells) and/or GABA_A receptor ligand, with potential for the treatment or prevention of disorders associated with NK₃ and/or GABA_A such as anxiety, depression, sleep disorders, cognitive impairment, drug addiction, schizophrenia, obesity, chronic pulmonary obstructive disorder or pain. Another exemplified compound from this series of 4-substituted quinoline derivatives is:



295380: C27 H25 N3 O

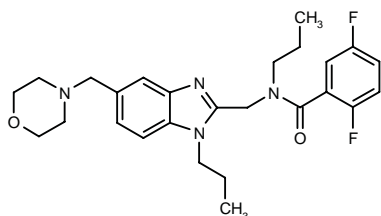
SOURCE – Neurogen.

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295589

2,5-Difluoro-*N*-[5-(4-morpholinylmethyl)-1-propyl-1*H*-benzimidazol-2-ylmethyl]-*N*-propylbenzamide



C26 H32 F2 N4 O2; Mol wt: 470.5608

ACTION – Selective modulator of brain GABA_A receptors, potentially useful for the treatment of anxiety, benzodiazepine overdose, Down's syndrome, depression and sleep, seizure and cognition disorders.

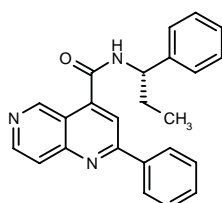
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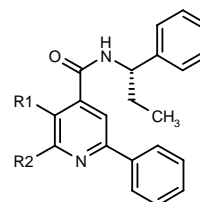
295609

2-Phenyl-*N*-[1(*S*)-phenylpropyl]-1,6-naphthyridine-4-carboxamide



C24 H21 N3 O; Mol wt: 367.4499

ACTION – Agent that binds to cell-surface receptors, in particular tachykinin NK₃ receptors (IC₅₀ = 0.05 μM). Potentially useful for the treatment of anxiety, depression, schizophrenia, obesity, pain and chronic obstructive pulmonary disorder. Other exemplified aryl fused 2,4-disubstituted pyridines are:



Compound	R1,R2	Formula
295611	-SCH=CH-	C ₂₃ H ₂₀ N ₂ OS
295612	-CH=CHCH=N-	C ₂₄ H ₂₁ N ₃ O

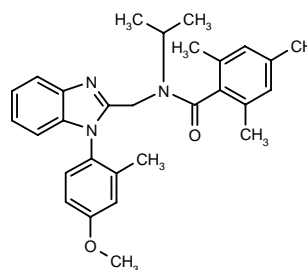
SOURCE – Neurogen.

REFERENCES

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295633

N-Isopropyl-*N*-[1-(4-methoxy-2-methylphenyl)-1*H*-benzimidazol-2-ylmethyl]-2,4,6-trimethylbenzamide



C29 H33 N3 O2; Mol wt: 455.5987

ACTION – Selective modulator of corticotropin-releasing factor CRF₁ receptors, expected to be useful for the treatment of stress, anxiety, depression, obesity, cardiovascular diseases and eating disorders.

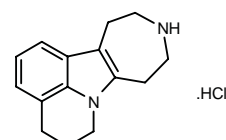
SOURCE – Neurogen.

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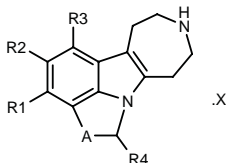
296524

5,6,9,10,11,12-Hexahydro-4*H*,8*H*-azepino[4',5':4,5]-pyrrolo[3,2,1-*ij*]quinoline hydrochloride



C15 H18 N2 . HCl; Mol wt: 262.7821

ACTION – 5-HT receptor ligand, expected to be useful for the treatment of a variety of CNS disorders and specifically claimed for the treatment or prevention of anxiety, obesity, depression and stress-related diseases. Other exemplified tetracyclic azepinoindole compounds include the following:



Compound	R1	R2	R3	R4	A	X	Formula
296526	H	H	H	Me	-(CH ₂) ₂ -	HCl	C ₁₆ H ₂₀ N ₂ ·HCl
296527	H	H	H	H	-CH ₂ CH(Me)-	HCl	C ₁₆ H ₂₀ N ₂ ·HCl
296528	H	F	H	H	-CH ₂ -	HCl	C ₁₄ H ₁₅ FN ₂ ·HCl
296529	H	H	Me	H	-OCH ₂ -	HCl	C ₁₅ H ₁₈ N ₂ O·HCl
296530	H	H	F	H	-OCH ₂ -	HCl	C ₁₄ H ₁₅ FN ₂ O·HCl
296531	Cl	H	H	H	-OCH ₂ -	fumarate	C ₁₄ H ₁₅ ClN ₂ O·C ₄ H ₄ O ₄
296532	H	F	Cl	H	-OCH ₂ -	fumarate	C ₁₄ H ₁₄ ClFN ₂ O·C ₄ H ₄ O ₄
296533	H	H	Cl	H	-CH ₂ -	fumarate	C ₁₄ H ₁₅ ClN ₂ ·C ₄ H ₄ O ₄
296534	H	F	H	Me	-COCH ₂ -	oxalate	C ₁₆ H ₁₇ FN ₂ O·C ₂ H ₂ O ₄
296535	H	H	H	H	-CH(OMe)CH ₂ -		C ₁₆ H ₂₀ N ₂ O

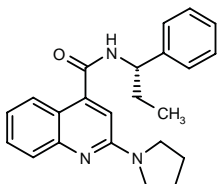
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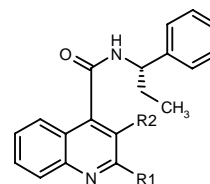
296571

N-[1(*S*)-Phenylpropyl]-2-(1-pyrrolidinyl)quinoline-4-carboxamide



C₂₃ H₂₅ N₃ O; Mol wt: 359.4705

ACTION – Selective neurokinin NK₃ receptor antagonist with potential for the treatment of a broad range of disorders including depression, anxiety, schizophrenia, obesity, pain, Parkinson's disease, Alzheimer's disease, neurodegenerative disorders, movement disorders, respiratory diseases, inflammatory diseases, neuropathy, immune disorders, migraine, biliary dysfunction and dermatitis. Other specifically claimed compounds from this series of 2-aminoquinolinecarboxamide derivatives include the following:



Compound	R1	R2	Formula
296572	N(Me)CH ₂ Ph	H	C ₂₇ H ₂₇ N ₃ O
296573	4-Me-1-Pip	H	C ₂₅ H ₂₉ N ₃ O
296574	2-Me-1-Pip	H	C ₂₅ H ₂₉ N ₃ O
296575	4-Me-1-Piz	H	C ₂₄ H ₂₈ N ₄ O
296576	3-(CH ₂ OH)-1-Pip	H	C ₂₅ H ₂₉ N ₃ O ₂
296577	1-pyrrolidinyl	Me	C ₂₄ H ₂₇ N ₃ O
296578	1-Pip	OMe	C ₂₅ H ₂₉ N ₃ O ₂

SOURCE – Neurogen.

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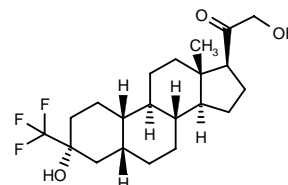
Co-2-6749

250872

3 α ,21-Dihydroxy-3 β -(trifluoromethyl)-19-nor-5 β -pregnan-20-one

GMA-839

WAY-141839



C₂₁ H₃₁ F₃ O₃; Mol wt: 388.4669

ACTION – Neuroactive steroid with moderate binding affinity for GABA_A receptors in rat brain cortical membranes (IC₅₀ = 230 nM) and high affinity for the α 3 β 2 γ 2L subtype (IC₅₀ = 96 nM); at concentrations up to 10 μ M, it did not interfere with other receptors including cytosolic steroid, inhibitory and excitatory amino acid, monoamine and peptide receptors. *In vivo*, compound induced a dose-dependent increase in punished responding in rats, pigeons and squirrel monkeys, consistent with anxiolytic-like activity. Particularly, in rats, compound showed a minimum effective dose (MED) of 1.6 mg/kg p.o. for increasing punished responding and was more active than the reference compound alprazolam (MED = 8.1 mg/kg p.o.). It also showed a large separation between the MED and the behavioral suppressive dose (therapeutic index [TI] = 8.3) in rats, as well as between the MED and the ataxic dose in the rotarod test (TI = 15.8). In pigeons and squirrel monkeys, it increased punished responding (784% at 30 mg/kg p.o. and 1774% at 10 mg/kg p.o., respectively), with no effect on unpunished responding at effective doses. No tolerance developed in rats after 14 days' repeated administration, and a minimal interaction with ethanol was seen in the rotarod test. Potentially useful for the treatment of chronic anxiety disorders.

SOURCES – CoCensys; Wyeth-Ayerst.

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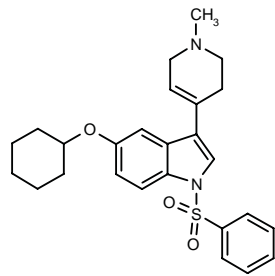
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ANTIPSYCHOTIC DRUGS

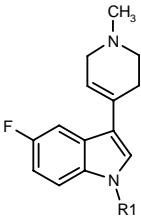
295332

5-(Cyclohexyloxy)-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(phenylsulfonyl)-1H-indole



C26 H30 N2 O3 S; Mol wt: 450.6000

ACTION – 5-HT₆ receptor antagonist with potential for the treatment of CNS disorders, particularly schizophrenia. Compound exhibited high affinity for human 5-HT₆ receptors (K_i < 50 nM) and at least 300-fold greater affinity relative to human 5-HT_{2C} and 5-HT₇ receptors; antagonist activity at 5-HT₆ receptors was demonstrated by inhibition of 5-HT-induced cAMP accumulation in transfected HEK293 cells. Other exemplified compounds from this series of piperidine-indole compounds include the following:



Compound	R1	Formula
295333	1-Naph-SO2	C ₂₄ H ₂₁ FN ₂ O ₂ S
295334	SO2Ph	C ₂₀ H ₁₉ FN ₂ O ₂ S
295337	2-Cl-PhCO	C ₂₁ H ₁₈ ClFN ₂ O

SOURCE – NPS Allelix.

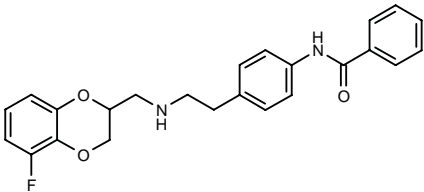
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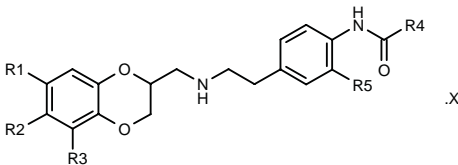
295421

N-[4-[2-(5-Fluoro-2,3-dihydro-1,4-benzodioxin-2-ylmethyl-amino)ethyl]phenyl]benzamide



C24 H23 F N2 O3; Mol wt: 406.4547

ACTION – High-affinity dopamine D3 receptor ligand with low or moderate affinity for dopamine D2 and 5-HT_{1A} receptors. As such, this compound may be indicated for the treatment of psychosis, anxiety, panic attacks, phobia, obsessive–compulsive disorders, depression, drug abuse, sexual dysfunction, eating disorders and migraine, as well as Alzheimer’s disease or age-related cognition disorders and Parkinson’s disease. Other exemplified N-[2-(4-aminophenyl)ethyl-2,3-dihydro-1,4-benzodioxine-2-methanamines are:



Compound	R1	R2	R3	R4	R5	X	Formula
295422	H	H	F	NHCH2-CH2OMe	H	fumarate	C ₂₁ H ₂₆ FN ₃ O ₄ ·C ₄ H ₄ O ₄
295423	H	H	Br	Me	H	fumarate	C ₁₉ H ₂₁ BrN ₃ O ₃ ·C ₄ H ₄ O ₄
295424	CN	H	H	Me	H	HCl	C ₂₀ H ₂₁ N ₃ O ₃ ·HCl
295425	H	CO2Et	H	Me	H	maleate	C ₂₂ H ₂₆ N ₂ O ₅ ·C ₄ H ₄ O ₄
295426	CN	H	H	-(CH2)2-		HCl	C ₂₁ H ₂₁ N ₃ O ₃ ·HCl

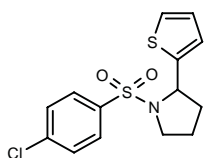
SOURCE – Sanofi-Synthélabo.

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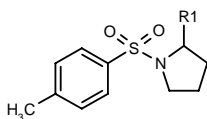
295453

1-(4-Chlorophenylsulfonyl)-2-(2-thienyl)pyrrolidine



C₁₄ H₁₄ Cl N O₂ S₂; Mol wt: 327.8546

ACTION – Metabotropic glutamate type I receptor antagonist (IC₅₀ = 0.56 μM), potentially useful for the treatment of acute and chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits. Other specifically claimed 1-arylsulfonyl-2-aryl-pyrrolidine derivatives are:



Compound	R1	Formula
295454	2-thienyl	C ₁₅ H ₁₇ NO ₂ S ₂
295455	3-thienyl	C ₁₅ H ₁₇ NO ₂ S ₂

The invention also includes compounds that act as agonists at metabotropic glutamate receptors.

SOURCE – Roche.

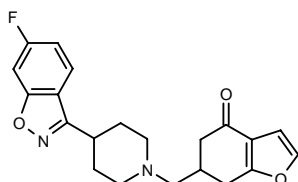
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QF-1004B²

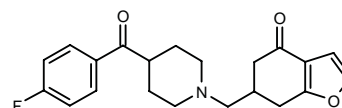
296397

6-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-ylmethyl]-6,7-dihydrobenzofuran-4(5H)-one



C₂₁ H₂₁ F N₂ O₃; Mol wt: 368.4059

ACTION – Antipsychotic agent with a relatively low capacity to induce extrapyramidal side effects (EPS); it displays high affinity for 5-HT_{2A} and dopamine D₁, D₂ and D₄ receptors (pK_i = 7.97, 7.54, 8.02 and 7.68, respectively), moderate affinity for 5-HT_{2B} receptors (pK_i = 6.61) and low affinity for 5-HT_{2C} receptors (pK_i = 4.74). Compound significantly increased striatal levels of dopamine metabolites in rats following injection at a dose of 10 mg/kg. Behavioral effects in rats and mice were consistent with dopamine receptor blockade in the limbic region, i.e., a reduction in spontaneous motility (ED₅₀ = 0.48 mg/kg i.p.), *d*-amphetamine-induced hypermotility and apomorphine-induced climbing (ED₅₀ = 0.34 mg/kg i.p.), as well as in striatum, i.e., induction of catalepsy in mice (ED₅₀ = 3.84 mg/kg i.p.). Another conformationally constrained butyrophenone is:



QF-1003B [296396]^{1,2}: C₂₁ H₂₂ F N O₃

SOURCES – Universidad de Santiago de Compostela, Santiago de Compostela (ES); Università degli Studi di Pisa, Pisa (IT).

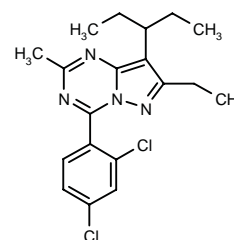
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TREATMENT OF MOOD DISORDERS

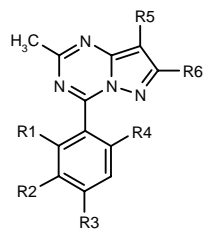
295543

4-(2,4-Dichlorophenyl)-7-ethyl-8-(1-ethylpropyl)-2-methylpyrazolo[1,5-*a*][1,3,5]triazine



C₁₉ H₂₂ Cl₂ N₄; Mol wt: 377.3168

ACTION – Corticotropin-releasing factor (CRF) antagonist, potentially useful for the treatment of psychiatric, neurological and immunological disorders, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbances and stress. The preferred use is the treatment of depression and anxiety. Other exemplified pyrazolotriazines are:



Compound	R1	R2	R3	R4	R5	R6	Formula
295544	H	H	Cl	Cl	CH(Me)OMe	Et	C ₁₇ H ₁₈ Cl ₂ N ₄ O
295545	Me	H	Me	Me	CH(Et)2	Et	C ₂₂ H ₃₀ N ₄
295546	H	H	OMe	Me	NHCH(CH ₂ OMe) ₂	Et	C ₂₁ H ₂₉ N ₅ O ₃
295547	H	H	OMe	Me	cycobutyl-CH(Me)	Et	C ₂₂ H ₂₈ N ₄ O
295548	H	H	OMe	Cl	3-Pyr-C(OH)(Ph)	Et	C ₂₇ H ₂₄ ClN ₅ O ₂
295550	H	H	Cl	Cl	OCH(Et)CH ₂ OMe	OMe	C ₁₈ H ₂₀ Cl ₂ N ₄ O ₃
295551	H	H	Cl	Cl	cyclopropyl-CH(OMe)	OMe	C ₁₈ H ₁₈ Cl ₂ N ₄ O ₂
295552	H	F	OMe	Cl	CH(Et)CH ₂ CH ₂ OMe	Et	C ₂₁ H ₂₆ ClFN ₄ O ₂
295554	H	OMe	OMe	Cl	CH(Et)2	OH	C ₁₉ H ₂₃ ClN ₄ O ₃

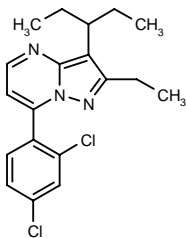
SOURCE – DuPont Pharmaceuticals.

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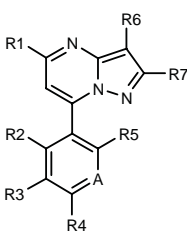
295559

7-(2,4-Dichlorophenyl)-2-ethyl-3-(1-ethylpropyl)pyrazolo-[1,5-a]pyrimidine



C19 H21 Cl2 N3; Mol wt: 362.3019

ACTION – Corticotropin-releasing factor (CRF) antagonist, potentially useful for the treatment of psychiatric, neurological and immunological disorders, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress. The preferred use is the treatment of depression and anxiety. Other exemplified pyrazolopyrimidines are:



Compound	R1	R2	R3	R4	R5	R6	R7	A	Formula
295562	Me	Me	H	N(Me)2	H	CH(Et)Bu	Et	N	C ₂₄ H ₃₅ N ₅
295563	Me	Me	H	N(Me)2	H	CH(Et)2	OMe	N	C ₂₁ H ₂₉ N ₅ O
295564	Me	Me	H	N(Me)2	H	N(Et)2	OMe	N	C ₂₀ H ₂₈ N ₆ O
295566	H	OMe	H	OMe	OMe	C(vinyl)2Me	Et	CH	C ₂₃ H ₂₇ N ₃ O ₃
295567	H	H	F	OMe	Cl	CH(Et)2	Et	CH	C ₂₀ H ₂₃ ClFN ₃ O
295568	H	H	H	OMe	Me	CH(Et)Bu	Et	CH	C ₂₃ H ₃₁ N ₃ O
295569	H	H	H	Cl	Cl	CH(Me)-CH ₂ OMe	OMe	CH	C ₁₇ H ₁₇ Cl ₂ N ₃ O ₂
295570	H	H	F	Cl	Cl	CH(Me)-CH ₂ OEt	OMe	CH	C ₁₈ H ₁₈ Cl ₂ FN ₃ O ₂
295572	H	H	H	CF ₃	Cl	CH(Me)-CH ₂ OMe	Et	CH	C ₁₉ H ₁₉ ClF ₃ N ₃ O

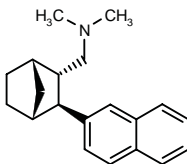
SOURCE – DuPont Pharmaceuticals.

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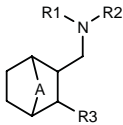
296025

N,N-Dimethyl-N-[3exo-(2-naphthyl)bicyclo[2.2.1]hept-2endo-ylmethyl]amine



C20 H25 N; Mol wt: 279.4245

ACTION – 5-HT reuptake inhibitor displaying a K_i < 100 nM when tested for displacement of [³H]-citalopram from binding sites on rat cerebral cortical membranes. Potentially useful for the treatment of a variety of disorders such as depression, obesity, bulimia, alcoholism, pain, hypertension, aging, senile dementia, Alzheimer's disease, memory loss, attention deficit hyperactivity disorder, sexual dysfunction, anxiety, chronic fatigue syndrome, panic, obsessive-compulsive disorder, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis and sleep disorders. Other exemplified 3-bicycloaryl-2-aminomethyl-bicycloalkanes are:



Compound	R1	R2	R3	A	Isomer	Formula
296026	Me	Me	2-Naph	-CH2-	3endo,2exo	C ₂₀ H ₂₅ N
296027	Me	Me	2-Naph	-CH2-	cis	C ₂₀ H ₂₅ N
296028	Me	Me	6-F-2-Naph	-CH2-	1S,2S,3S,4R	C ₂₀ H ₂₄ FN
296029	Me	Me	6-benzothienyl	-CH2-	1S,2S,3S,4R	C ₁₈ H ₂₃ NS
296030	Me	Me	3-Me-5-benzothieryl	-CH2-	1R,2R,3R,4S	C ₁₉ H ₂₅ NS
296031	Me	Me	6-F-3-benzothieryl	-CH2-	1S,2S,3S,4R	C ₁₈ H ₂₂ FNS
296032	Me	Me	6-F-2-benzothieryl	-CH2-	1S,2S,3S,4R	C ₁₈ H ₂₂ FNS
296033	Me	H	2-Naph	-CH2-	2endo,3exo	C ₁₉ H ₂₃ N
296034	H	H	2-Naph	-(CH2)2-	trans	C ₁₉ H ₂₃ N
296035	H	H	2-Naph	-(CH2)2-	cis	C ₁₉ H ₂₃ N

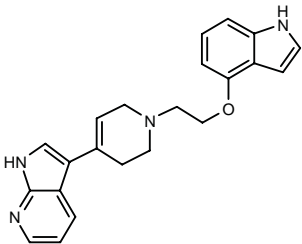
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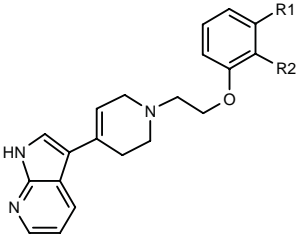
296563

3-[1-[2-(1*H*-Indol-4-yloxy)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine



C22 H22 N4 O; Mol wt: 358.4428

ACTION – Antidepressant with high affinity for 5-HT_{1A} receptors (*K*_i = 10.9 nM for displacement of [³H]-8-OH-DPAT binding in CHO cells stably transfected with the human receptor) and which also inhibits the 5-HT transporter (*K*_i = 1.46 nM for displacement of [³H]-paroxetine binding to the 5-HT transporter from rat cortical membranes). Other specifically claimed compounds from this series of azaindole derivatives are:



Compound	R1	R2	Formula
296564	-OCH2CH2O-		C ₂₂ H ₂₃ N ₃ O ₃
296565	-N=CHCH=CH-		C ₂₃ H ₂₂ N ₄ O

SOURCE – American Home Products.

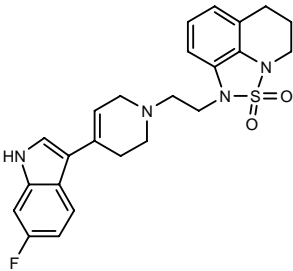
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LY-367265

296940

1-[2-[4-(6-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]-5,6-dihydro-1*H*,4*H*-[1,2,5]thiadiazolo-[4,3,2-*i*]quinoline 2,2-dioxide



C24 H25 F N4 O2 S; Mol wt: 452.5515

ACTION – Potential antidepressant, a potent antagonist of both the 5-HT transporter and the 5-HT_{2A} receptor. Compound exhibited high affinity for the 5-HT transporter in rat cortex (*K*_i = 2.3 nM) and potently and selectively inhibited [³H]-5-HT uptake into rat cortical synaptosomes (*IC*₅₀ = 3.1 nM) as compared to [³H]-noradrenaline uptake (*IC*₅₀ >1000 nM). It also displayed high affinity for the human 5-HT_{2A} receptor (*K*_i = 0.81 nM), but little activity at 5-HT_{1B} and 5-HT_{1D} receptors. Expected to be associated with a low incidence of side effects such as sleep disorders and diminished sexual function compared to selective serotonin reuptake inhibitors (SSRI).

SOURCE – Lilly.

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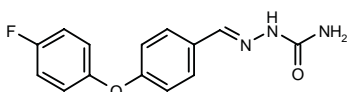
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

Co-102862*

246696

4-(4-Fluorophenoxy)benzaldehyde semicarbazone



C14 H12 F N3 O2; Mol wt: 273.2690

ACTION – Potent non-sedating anticonvulsant, a selective neuronal voltage-gated sodium channel blocker with selectivity for inactivated states of the channel versus resting states. Compound showed potent and long-lasting anticonvulsant activity following oral administration in several preclinical models including maximal electro-shock-induced seizures in mice and rats (ED_{50} = 2.0 and 1.5 mg/kg p.o., respectively), corneal kindling-induced fully kindled stage 5 seizures in rats (ED_{50} = 3.9 mg/kg p.o.) and fully kindled hippocampal seizures, where it reduced afterdischarge duration. Compound also exhibited antinociceptive effects in the formalin test in mice (ED_{50} = 5-10 mg/kg p.o.). No dose-limiting side effects were observed in preclinical models even at doses 10-40 times greater than those required for therapeutic effect. Potentially useful for the treatment of generalized tonic-clonic and complex partial seizure disorders and for the treatment of chronic pain.

SOURCES – CoCensys; University of Saskatchewan, Saskatoon, SK (CA).

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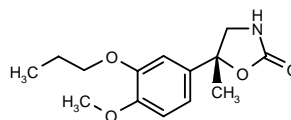
*Identified compound 246696 Drug Data Rep 1997, 019(04): 0306.

THERAPY OF IMMUNOLOGICAL NEUROMUSCULAR DISORDERS

MESOPRAM*

251857

(-)-(R)-5-(4-Methoxy-3-propoxyphenyl)-5-methyloxazolidin-2-one



C14 H19 N O4; Mol wt: 265.3120

ACTION – Potent and selective phosphodiesterase type 4 (PDE4) inhibitor proven to inhibit interferon gamma but not IL-5 production by activated human T-cells. In murine T-helper cell clones, compound induced a downregulation of the Th1 cytokine interferon gamma but not of the Th2 cytokines IL-4 and IL-5. *In vivo*, it demonstrated good efficacy in acute, chronic and relapsing-remitting models of experimental autoimmune encephalomyelitis (EAE). In particular, in the acute EAE model in rats, compound induced dose-dependent suppression of the clinical signs, as well as a reduction in spinal cord and brain inflammatory lesions and brain interferon gamma and TNF- α expression; complete prevention of the development of disease was seen at 1.0 mg/kg/day i.p. Phase I clinical trials provided evidence of immune system modulation in the absence of side effects. Potentially useful for the treatment of multiple sclerosis.

SOURCE – Schering AG.

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- *Identified compound **251857** (see **251749**) Drug Data Rep 1997, 019(08): 0695.

MITOXANTRONE HYDROCHLORIDE

Rec INN; USAN

New use

091234

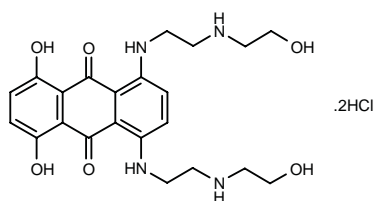
1,4-Dihydroxy-5,8-bis[2-(2-hydroxyethylamino)-ethylamino]-9,10-anthracenedione dihydrochloride

CL-232315

DAD

Mitozantrone hydrochloride (BANM)

NSC-301739



C₂₂ H₂₈ N₄ O₆ · 2HCl; Mol wt: 517.4070

ACTION – Synthetic anthracenedione first approved for use in combination with corticosteroids to treat pain in patients with advanced hormone-refractory prostate cancer and for initial therapy of acute nonlymphocytic leukemia.

INDICATION – Reduction of neurological disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing or worsening relapsing–remitting multiple sclerosis.

PRESENTATION – Sterile aqueous solution (concentrate for dilution prior to use) for i.v. infusion, containing mitoxantrone hydrochloride equivalent to 2 mg/ml free base in multidose vials of 10 ml (20 mg), 12.5 ml (25 mg) and 15 ml (30 mg).

PROPRIETARY NAME – Novantrone (US).

SOURCE – Immunex.

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ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

BOTULINUM TOXIN TYPE B⁺

215951

Botulin toxin B

AN-072

BoNT/B

BTX-B

BotBTM (former brand name)

NeuroBloc[®] (EU)

ACTION – Neurotoxin that inhibits acetylcholine release at the neuromuscular junction.

INDICATIONS – Treatment of cervical dystonia to reduce the severity of abnormal head position and neck pain.

PRESENTATION – Single-use vials (3.5 ml) of injectable solution, 5000 U/ml; one unit corresponds to the calculated median lethal i.p. dose in mice.

PROPRIETARY NAME – MyoBloc (US).

SOURCE – Elan.

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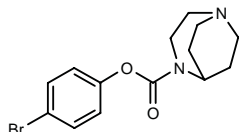
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TREATMENT OF DISORDERS OF COGNITION

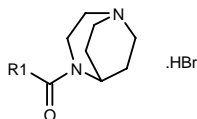
295437

1,4-Diazabicyclo[3.2.2]nonane-4-carboxylic acid 4-bromophenyl ester



C₁₄ H₁₇ Br N₂ O₂; Mol wt: 325.2043

ACTION – Agent with affinity for the $\alpha 7$ subunit of nicotinic acetylcholine receptors, expected to be useful for the treatment of CNS and gastrointestinal disorders including cognition disorders, Parkinson's disease, neurodegenerative diseases, psychiatric disorders, Crohn's disease, ulcerative colitis, irritable bowel syndrome and obesity. Other exemplified 1,4-diazabicyclo[3.2.2]nonane derivatives are:



Compound	R1	Formula
295438	NHPh	C ₁₄ H ₁₉ N ₃ O.HBr
295439	N(Me)Ph	C ₁₅ H ₂₁ N ₃ O.HBr
295440	4-Ph-PhO	C ₂₀ H ₂₂ N ₂ O ₂ .HBr

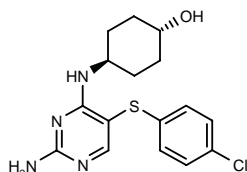
SOURCE – Sanofi-Synthélabo.

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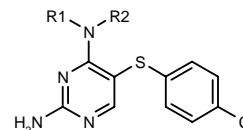
295644

trans-4-[2-Amino-5-(4-chlorophenylsulfanyl)pyrimidin-4-ylamino]cyclohexanol



C₁₆ H₁₉ Cl N₄ O S; Mol wt: 350.8721

ACTION – Neurotrophic agent proven to enhance nerve growth factor (NGF)-stimulated neurite outgrowth and to increase the activity of choline acetyltransferase (ChAT) in PC12 cells, doubling ChAT activity over the activity of NGF alone at 0.04 μ M. Based on this profile, the compound is expected to be useful for the treatment of neurodegenerative or neurological disorders, preferably Alzheimer's disease, senile dementia and peripheral neuropathy. Other exemplified substituted pyrimidines include the following:



Compound	R1	R2	Formula
295645	CH ₂ CH ₂ OH	H	C ₁₂ H ₁₃ ClN ₄ OS
295646	-CH ₂ CH ₂ N(Ac)CH ₂ CH ₂ -		C ₁₆ H ₁₈ ClN ₅ OS
295647	4-OH-Ph	H	C ₁₆ H ₁₃ ClN ₄ OS
295648	4-AcO-Ph	H	C ₁₈ H ₁₅ ClN ₄ O ₂ S

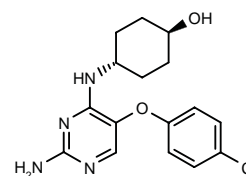
SOURCE – Krenitsky Pharmaceuticals.

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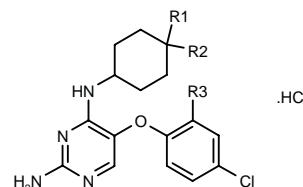
296009

trans-4-[2-Amino-5-(4-chlorophenoxy)pyrimidin-4-ylamino]cyclohexanol



C₁₆ H₁₉ Cl N₄ O₂; Mol wt: 334.8051

ACTION – Neurotrophic agent with nerve growth factor (NGF)-like activity proven to enhance NGF-stimulated neurite outgrowth and increase the activity of choline acetyltransferase (ChAT) in PC12 cells, doubling ChAT activity over the activity of NGF alone at 0.4 μ M. Potentially useful for the treatment of neurodegenerative or neurological disorders, preferably Alzheimer's disease, senile dementia and peripheral neuropathy. Other exemplified substituted pyrimidines are:



Compound	R1	R2	R3	Isomer	Formula
296010	OH	H	Cl	trans	C ₁₆ H ₁₈ Cl ₂ N ₄ O ₂ .HCl
296011	-O-	H			C ₁₆ H ₁₇ ClN ₄ O ₂ .HCl

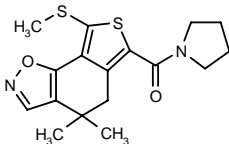
SOURCE – Krenitsky Pharmaceuticals.

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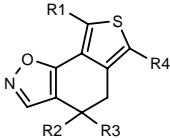
296108

1-[4,4-Dimethyl-8-(methylsulfanyl)-4,5-dihydrothieno-[3,4-g][1,2]benzisoxazol-6-yl]-1-(1-pyrrolidiny)methanone



C17 H20 N2 O2 S2; Mol wt: 348.4890

ACTION – Selective ligand for the α5 subunit of the GABA_A receptor, exhibiting a K_i value of 300 nM or less for displacement of [³H]-flumazenil from human GABA_A receptors containing the α5 subunit expressed in Ltk cells. Potentially useful for the treatment of cognition disorders such as Alzheimer’s disease. Other exemplified substituted thienobenzisoxazole derivatives are:



Compound	R1	R2=R3	R4	Formula
296109	SMe	Me	CON(Me)2	C ₁₅ H ₁₈ N ₂ O ₂ S ₂
296110	SMe	Me	cyclohexyl-N(Me)CH(OH)	C ₂₀ H ₂₈ N ₂ O ₂ S ₂
296111	OEt	Me	1-pyrrolidinyl-CO	C ₁₈ H ₂₂ N ₂ O ₃ S
296112	SMe	Me	perhydro-1-azepinyl	C ₁₉ H ₂₄ N ₂ O ₂ S ₂
296113	i-PrS	Me	1-pyrrolidinyl-CO	C ₁₉ H ₂₄ N ₂ O ₂ S ₂
296115	SMe	Me	4-morpholinyl-CO	C ₁₇ H ₂₀ N ₂ O ₃ S ₂
296116	SMe	Me	4-Me-1-Piz-CO	C ₁₈ H ₂₃ N ₃ O ₂ S ₂
296117	SMe	H	2-thiazolyl	C ₁₃ H ₁₀ N ₂ OS ₃
296118	SPh	Me	1-pyrrolidinyl-CO	C ₂₂ H ₂₂ N ₂ O ₂ S ₂
296119	SEt	Me	1-pyrrolidinyl-CO	C ₁₈ H ₂₂ N ₂ O ₂ S ₂
296120	SPr	Me	1-pyrrolidinyl-CO	C ₁₉ H ₂₄ N ₂ O ₂ S ₂
296121	SMe	Me	2-Pyr	C ₁₇ H ₁₆ N ₂ OS ₂
296122	SMe	Me	3-Pyr	C ₁₇ H ₁₆ N ₂ OS ₂
296123	SMe	Me	1-Me-3-pyrazolyl	C ₁₆ H ₁₇ N ₃ OS ₂
296124	SMe	Me	1-Me-1,2,4-triazol-3-yl	C ₁₅ H ₁₆ N ₄ OS ₂

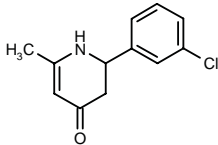
SOURCE – Merck Sharp & Dohme.

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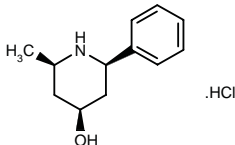
296438

(±)-2-(3-Chlorophenyl)-6-methyl-1,2,3,4-tetrahydropyridin-4-one



C12 H12 Cl N O; Mol wt: 221.6858

ACTION – Cognition-enhancing agent, potentially useful for the treatment of memory deficits related to cerebral aging and neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, Pick’s disease, Korsakoff’s syndrome and frontal or subcortical dementias. Another specifically claimed 1-aza-2-alkyl-6-aryl-cycloalkane is:



296439: C12 H17 N O . HCl

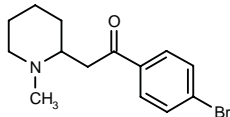
SOURCE – ADIR.

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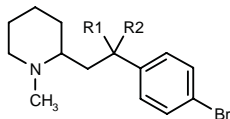
296451

1-(4-Bromophenyl)-2-(1-methylpiperidin-2-yl)ethan-1-one

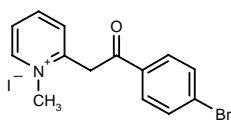


C14 H18 Br N O; Mol wt: 296.2062

ACTION – Cognition-enhancing agent, potentially useful for the treatment of memory deficits related to cerebral aging and neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, Pick’s disease, Korsakoff’s syndrome and frontal or subcortical dementias. Other specifically claimed compounds from this series of substituted pyridines and piperidines are:



Compound	R1	R2	Isomer	Formula
296452	-O-		R	C ₁₄ H ₁₈ BrNO
296453	-O-		S	C ₁₄ H ₁₈ BrNO
296454	H	OH		C ₁₄ H ₂₀ BrNO
296455	H	OH	S,S	C ₁₄ H ₂₀ BrNO
296457	H	OH	R,R	C ₁₄ H ₂₀ BrNO



296458: C₁₄ H₁₃ Br I N O

SOURCE – ADIR.

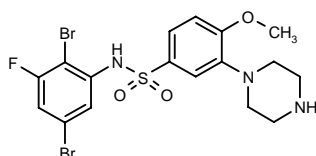
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SB-357134

298458

N-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-(1-piperazinyl)benzenesulfonamide



C₁₇ H₁₈ Br₂ F N₃ O₃ S; Mol wt: 523.2192

ACTION – Potent and selective serotonin 5-HT₆ receptor antagonist with pK_i value of 8.5 for affinity at 5-HT₆ receptors and 1,300-fold selectivity over other 5-HT receptors, dopamine D₂ and D₃ receptors and α_{1B}-adrenoceptors. Compound showed a favorable pharmacokinetic profile, with 82% oral bioavailability, low clearance (14 ml/min/kg) and good CNS penetration (19%). Potentially useful for the treatment of learning and memory disorders.

SOURCE – GlaxoSmithKline.

REFERENCES

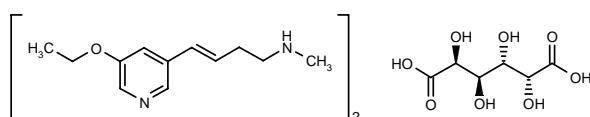
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2. Reavill, C.A. and Routledge, C. (SmithKline Beecham plc) *Use of 5HT₆ antagonists*. WO 0012073.
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4. Bromidge, S.M. et al. *Phenyl benzenesulfonamides are novel and selective 5-HT₆ antagonists: Identification of N-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (SB-357134)*. Bioorg Med Chem Lett 2001, 11(1): 55.

TC-2559

298805

4-(5-Ethoxypyridin-3-yl)-*N*-methyl-3(*E*)-buten-1-amine D-galactarate (2:1)

TC-2557 (sesquifumarate)



C₂₄ H₃₆ N₄ O₂ . C₆ H₁₀ O₈; Mol wt: 622.7114

ACTION – Neuronal nicotinic acetylcholine receptor agonist with marked selectivity for CNS versus peripheral nervous system receptors, showing nanomolar affinity for rat brain nicotinic receptors (K_i = 5 nM); it was found to activate neuronal nicotinic receptors with an EC₅₀ value of 203 nM for stimulation of dopamine release from rat striatal synaptosomes and an EC₅₀ value of 367 nM for stimulation ⁸⁶Rb⁺ efflux from rat thalamic synaptosomes. Compound exhibited high selectivity versus human muscle and ganglionic nicotinic acetylcholine receptors, with no activation at concentrations up to 1 mM. Both compound and nicotine at 10 μM showed significant neuroprotective effects against glutamate-induced neurotoxicity in cultured fetal rat brain cells. *In vivo*, compound was found to significantly attenuate scopolamine-induced amnesia in a step-through passive avoidance task in rats at doses of 3 and 6 μmol/kg s.c., and to enhance performance in a radial arm maze task. Unlike nicotine, compound did not induce hypothermia and did not enhance locomotor activity after repeated daily administration for 14 days. Selected for further evaluation as a potential therapeutic agent for neuro-degenerative diseases.

SOURCE – Targacept.

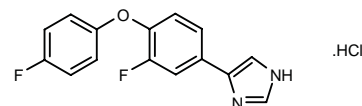
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4. Dull, G.M. et al. *[3-(5-Ethoxypyridinyl)-alkenyl 1 amine cpds*. US 5616716.
5. Bencherif, M. et al. *TC-2559: A novel orally active ligand selective at neuronal acetylcholine receptors*. Eur J Pharmacol 2000, 409(1): 45.

TREATMENT OF CEREBROVASCULAR DISEASES

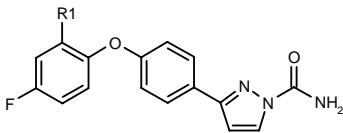
295427

4-[3-Fluoro-4-(4-fluorophenoxy)phenyl]-1*H*-imidazole hydrochloride



C₁₅ H₁₀ F₂ N₂ O . HCl; Mol wt: 308.7139

ACTION – Voltage-sensitive sodium channel blocker, as demonstrated by a K_i value of 0.25 μM for inhibition of voltage-gated sodium currents in HEK293 cells stably expressing the rBIIA isoform of Na⁺ channels. Anti-convulsant activity was demonstrated in the maximal electroshock seizure (MES) test in mice (ED₅₀ = 3.5 mg/kg p.o.). Potentially useful for the treatment of neuronal damage following global and focal ischemia, neurodegenerative conditions such as amyotrophic lateral sclerosis, tinnitus, diabetic neuropathy and pain, as well as for use as an antimanic depressant, local anesthetic, antiarrhythmic and anticonvulsant. Other specifically claimed compounds from this series of aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles include the following:



Compound	R1	Formula
295428	H	C ₁₈ H ₁₂ FN ₃ O ₂
295429	F	C ₁₈ H ₁₁ F ₂ N ₃ O ₂

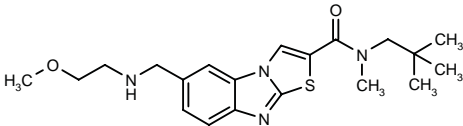
SOURCE – CoCensys.

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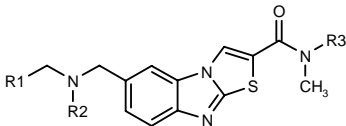
295634

N-(2,2-Dimethylpropyl)-6-(2-methoxyethylaminomethyl)-N-methylthiazolo[3,2-a]benzimidazole-2-carboxamide



C20 H28 N4 O2 S; Mol wt: 388.5332

ACTION – Agent with selective affinity for metabotropic glutamate receptors, reported to be useful for the treatment of stroke. Other specifically claimed thiazolo-benzimidazole derivatives are:



Compound	R1	R2	R3	Formula
295635	CH2OMe	H	cyclohexyl	C ₂₁ H ₂₈ N ₄ O ₂ S
295636	CH2CH2OMe	H	t-BuCH2	C ₂₁ H ₃₀ N ₄ O ₂ S
295637	-CH2OCH2CH2-		cyclohexyl	C ₂₂ H ₂₈ N ₄ O ₂ S
295638	H	CH2CO2Me	cyclohexyl	C ₂₂ H ₂₈ N ₄ O ₃ S
295639	H	CH2CH2OMe	t-BuCH2	C ₂₁ H ₃₀ N ₄ O ₂ S
295640	H	CH2CH2OMe	cyclohexyl	C ₂₂ H ₃₀ N ₄ O ₂ S
295641	H	CH2CO2H	cyclohexyl	C ₂₁ H ₂₆ N ₄ O ₃ S

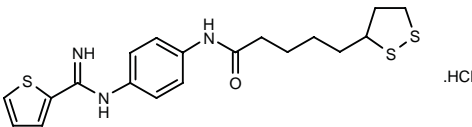
SOURCE – Yamanouchi.

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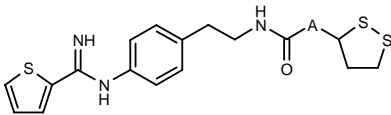
295649

5-(1,2-Dithiolan-3-yl)-N-[4-[1-imino-1-(2-thienyl)methyl-amino]phenyl]pentanamide hydrochloride

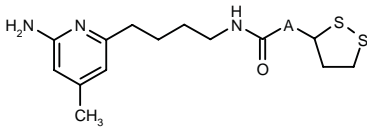


C19 H23 N3 O S3 . HCl; Mol wt: 442.0696

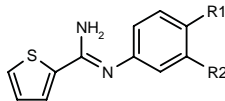
ACTION – A nitric oxide synthase (NOS) inhibitor also reported to enable the regeneration of antioxidants or entities trapping reactive oxygen species (ROS) and to intervene in a more general manner in the redox status of thiol groups. Compound inhibited constitutive neuronal enzyme (nNOS) from rat brain with an IC₅₀ of < 4.5 μM and protected murine hippocampal HT-22 cells from glutamate-induced oxidative stress with an IC₅₀ of < 30 μM. Potentially useful for the treatment of peripheral and central nervous system disorders such as Parkinson's disease, cognitive disorders, pain and drug addiction, as well as cerebrovascular disorders, inflammatory and proliferative disorders, vomiting, septic shock, transplant rejection, radiation damage, autoimmune diseases and cancer. Other specifically claimed compounds from this series of lipioic acid derivatives are:



Compound	A	Formula
295650	-(CH2)4-	C ₂₁ H ₂₇ N ₃ OS ₃
295651	-CH2-	C ₁₈ H ₂₁ N ₃ OS ₃



Compound	A	Formula
295652	-(CH2)4-	C ₁₈ H ₂₈ N ₃ OS ₂
295653	-CH2-	C ₁₅ H ₂₃ N ₃ OS ₂



Compound	R1	R2	Formula
295654	1,2-dithiolan-3-yl- -CH2CONH	H	C ₁₈ H ₁₇ N ₃ OS ₃
295655	1,2-dithiolan-3-yl- -(CH2)4CONHCH2	H	C ₂₀ H ₂₅ N ₃ OS ₃
295656	OMe	1,2-dithiolan-3-yl- -(CH2)4CONH	C ₂₀ H ₂₅ N ₃ O ₂ S ₃
295657	N(Me)2	1,2-dithiolan-3-yl- -(CH2)4CONHCH2	C ₂₂ H ₃₀ N ₄ OS ₃
295658	1-pyrrolyl	1,2-dithiolan-3-yl- -(CH2)4CONHCH2	C ₂₄ H ₂₈ N ₄ OS ₃

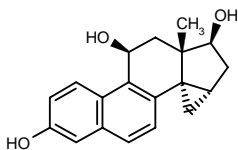
SOURCE – SCRAS.

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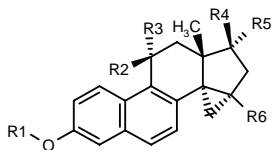
295719

14 α ,15 α -Methylenestra-1,3,5(10),6,8-pentaene-3,11 β ,17 β -triol



C₁₉ H₂₀ O₃; Mol wt: 296.3640

ACTION – Equilenine derivative with potent antioxidant activity and reduced systemic hormonal effects, potentially useful for the treatment of disorders where oxygen radical species are involved such as brain or spinal cord disorders, shock states, emphysema, ARDS, stroke, arteriosclerosis, ischemia, neurodegenerative disorders, asthma and muscular dystrophy, and particularly in geriatric prophylaxis in men and women. Other specifically claimed compounds from this series of 14,15- α -methylene equilenine derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
295721	COPh	OH	H	OH	H	H	C ₂₆ H ₂₄ O ₄
295722	COEt	OH	H	OH	H	H	C ₂₂ H ₂₄ O ₄
295724	H	OH	H	OCOC ₉ H ₁₉	H	H	C ₂₉ H ₃₆ O ₄
295726	H	OH	H	-O-	H	H	C ₁₉ H ₁₈ O ₃
295729	Me	H	OAc	OAc	H	H	C ₂₄ H ₂₆ O ₅
295730	H	OH	H	OH	H	Me	C ₂₀ H ₂₂ O ₃
295732	H	F	H	OH	H	H	C ₁₉ H ₁₉ FO ₂
295733	H	-O-	H	OH	H	H	C ₁₉ H ₁₈ O ₃
295734	Me	H	OAc	H	OAc	H	C ₂₄ H ₂₆ O ₅
295735	Me	-O-	H	H	OAc	H	C ₂₂ H ₂₂ O ₄
295736	COPh	OH	H	-CF ₂ -	H	H	C ₂₇ H ₂₂ F ₂ O ₃
295737	H	H	OH	-CH ₂ -	H	H	C ₂₀ H ₂₀ O ₂

SOURCE – Jenapharm.

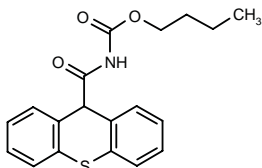
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296248

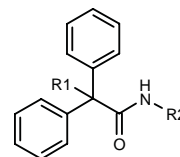
N-[10H-Dibenzo[b,e]thiopyran-10-ylcarbonyl]carbamic acid butyl ester

N-(9H-Thioxanthen-9-ylcarbonyl)carbamic acid butyl ester



C₁₉ H₁₉ N O₃ S; Mol wt: 341.4291

ACTION – A representative compound from a series of carbamic acid derivatives acting as agonists and/or antagonists of group I metabotropic glutamate receptors (mGluR, mglu). Compound displayed agonist activity in an *in vitro* assay using EBNA cells transfected with the rat mglu1a receptor, giving an EC₅₀ value of 0.14 μ M. Potentially useful in the treatment or prevention of acute and/or chronic neurological disorders including cerebral ischemia, spinal cord and head injuries, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, cognitive disorders, schizophrenia and Parkinson's disease. Other exemplified compounds include the following:



Compound	R1	R2	Formula
296249	H	cyclopropyl-CH ₂ OCO	C ₁₉ H ₁₉ NO ₃
296250	H	5-Me-2-oxazolyl	C ₁₈ H ₁₈ N ₂ O ₂
296251	Me	CO ₂ Me	C ₁₇ H ₁₇ NO ₃
296252	Me	allyl-OCO	C ₁₉ H ₁₉ NO ₃
296253	Me	CO ₂ Bu	C ₂₀ H ₂₃ NO ₃

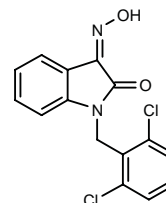
SOURCE – Roche.

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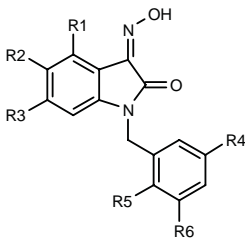
296513

1-(2,6-Dichlorobenzyl)-2,3-dihydro-1H-indole-2,3-dione 3-oxime



C₁₅ H₁₀ Cl₂ N₂ O₂; Mol wt: 321.1620

ACTION – Potent JNK protein kinase inhibitor, especially active in inhibiting JNK3 (K_i < 1 μ M). Potentially useful for the treatment or prevention of inflammatory and autoimmune diseases, destructive bone disorders, proliferative and neurodegenerative diseases, ischemia-reperfusion injury and angiogenesis-related conditions. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
296514	H	H	H	H	H	NO2	C ₁₈ H ₁₁ N ₃ O ₄
296515	H	H	Br	F	-OCH2OCH2-		C ₁₇ H ₁₂ BrFN ₂ O ₄
296516	Me	H	Me	F	-OCH2OCH2-		C ₁₉ H ₁₇ FN ₂ O ₄
296517	H	H	CH2Br	H	H	CO2Me	C ₁₈ H ₁₅ BrN ₂ O ₄
296518	H	H	NHCOPr	F	-OCH2OCH2-		C ₂₁ H ₂₀ FN ₃ O ₅
296519	H	H	NHCOPh	F	-OCH2OCH2-		C ₂₄ H ₁₈ FN ₃ O ₅
296520	H	H	NHSO2Et	F	-OCH2OCH2-		C ₁₉ H ₁₈ FN ₃ O ₆ S
296521	vinyl	H	H	F	-OCH2OCH2-		C ₁₉ H ₁₅ FN ₂ O ₄
296522	H	H	4-(CO2H-CH2CH2)-Ph	F	-OCH2OCH2-		C ₂₆ H ₂₁ FN ₂ O ₆
296523	H	2-Cl-Ph-CO	H	F	-OCH2OCH2-		C ₂₄ H ₁₆ ClFN ₂ O ₅

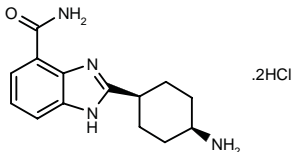
SOURCE – Vertex.

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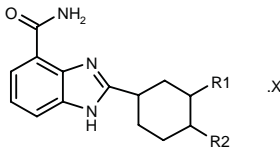
296546

cis-2-(4-Aminocyclohexyl)-1H-benzimidazole-4-carboxamide dihydrochloride



C14 H18 N4 O . 2HCl; Mol wt: 331.2450

ACTION – PARP (poly[ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase) inhibitor for the treatment of neurological and neurodegenerative disorders including cerebral ischemia, traumatic brain injury, stroke, Alzheimer's disease, Huntington's disease and epilepsy. Compound exhibits improved water solubility compared to previously reported PARP inhibitors, and is therefore suitable for i.v. administration; specifically, compound exhibited a water solubility of > 0.5% compared to a value of < 0.01% for the reference compound NU-1076. Other exemplified compounds from this series of cyclo-alkyl-substituted benzimidazoles include the following:



Compound	R1	R2	X	Formula
296547	OMe	H		C ₁₅ H ₁₉ N ₃ O ₂
296548	H	OMe		C ₁₅ H ₁₉ N ₃ O ₂
296549	H	OCH2CH2N(Et)2	2HCl	C ₂₀ H ₃₀ N ₄ O ₂ ·2HCl

SOURCE – BASF.

REFERENCES

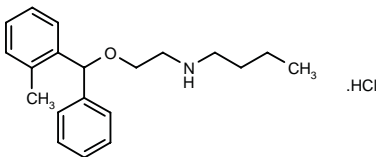
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LY-042826

266390

N-[2-[1-(2-Methylphenyl)-1-phenylmethoxy]ethyl]butan-1-amine hydrochloride

NCC-161



C20 H27 N O . HCl; Mol wt: 333.9002

ACTION – Neuronal calcium channel blocker proven to block KCl-induced calcium flux in HEK293 cells expressing human α 1A, α 1B and α 1E calcium channel subunits, and to block both KCl⁻ and veratridine-induced glutamate release *in vitro*. Compound (15 mg/kg i.p.) induced significant protection in global and focal cerebral ischemia models in gerbils when administered 30 min prior to or immediately after occlusion. At this dose it also provided significant neuroprotection in the ET-1 model of focal cerebral ischemia in rats when given immediately and 3 h after occlusion; the degree of protection was similar to that observed with MK-801 given immediately after occlusion at the dose of 2.5 mg/kg. Potentially useful as an antiischemic agent.

SOURCE – Lilly.

REFERENCES

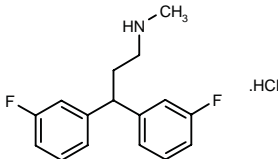
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NPS-1506*

285766

N-[3,3-Bis(3-fluorophenyl)propyl]-N-methylamine hydrochloride



C16 H17 F2 N . HCl; Mol wt: 297.7742

ACTION – Neuroprotective agent with moderate affinity for and uncompetitive antagonist activity at the NMDA receptor, as demonstrated in binding (IC_{50} = 664 nM for displacement of [3H]-MK-801 binding in rat cortical membranes) and functional studies (IC_{50} = 476 nM for inhibition of NMDA/glycine-induced increases in cytosolic calcium in rat cerebellar granule cells); its effects are consistent with open channel block. Compound showed neuroprotective efficacy in several models of stroke and head trauma in rats at doses ranging from 0.1 to 1 mg/kg i.v. or i.p., even when treatment was delayed 2 h after the onset of ischemia. Moreover, it did not elicit MK-801-like behavior or phencyclidine-like psychotomimetic effects at doses greater than those producing neuroprotection; the major side effect at higher doses in rats and dogs given single or multiple doses was whole-body tremors. In a phase I clinical study in healthy volunteers, compound was well tolerated at doses of 5-100 mg by single i.v. infusion and provided plasma levels in excess of those required for neuroprotection in rodents (8-80 ng/ml). Adverse events observed at the highest dose included mild dizziness, lightheadedness and mild to moderate ataxia, but PCP-like psychotomimetic or cardiovascular effects were not observed. Compound showed a very large volume of distribution at steady state and long half-life (about 60 h), indicating that a single i.v. dose may provide prolonged neuroprotection. A phase Ib trial in stroke patients is ongoing.

SOURCE – NPS Pharmaceuticals.

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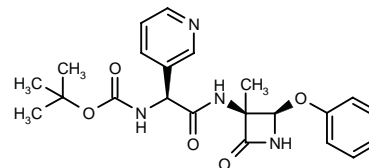
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6. Mueller, A.L. et al. *NPS 1506, a moderate affinity uncompetitive NMDA receptor antagonist: Preclinical summary and clinical experience*. Amino Acids 1999, 17(1): 11.
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8. Mueller, A.L. et al. *NPS 1506, a novel NMDA receptor antagonist and neuroprotectant. Review of preclinical and clinical studies*. Ann New York Acad Sci 1999, 890: 450.
9. *Company Profile: NPS Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) 1997, Dec 30.
10. *NPS Pharmaceuticals: Q4 and year-end 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1999, Feb 16.
11. NPS Pharmaceuticals, Inc. Annual Report 1995.

*Identified compound **285766** Drug Data Rep 2000, 022(05): 0408.

MISCELLANEOUS NEUROLOGIC DRUGS

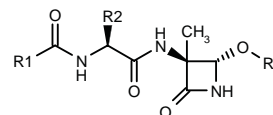
295723

N-[2-[3(*S*)-Methyl-2-oxo-4(*R*)-phenoxyazetidin-3-ylamino]-2-oxo-1(*S*)-(3-pyridyl)ethyl]carbamic acid *tert*-butyl ester



C22 H26 N4 O5; Mol wt: 426.4704

ACTION – Inhibitor of cysteine proteases, particularly cathepsins (IC_{50} = 0.36, 0.45, 1.34 and 0.05 μ M for inhibition of cathepsins B, L, K and S, respectively). Potentially useful for the treatment of muscular dystrophy, osteoporosis, tumor metastasis, rheumatoid arthritis, neuronal or cardiac ischemia, allergic immune response and protozoal or bacterial diseases. Other exemplified substituted azetidin-2-ones include the following:



Compound	R1	R2	R3	Formula
295725	CH ₂ CH ₂ Ph	CH ₂ Ph	Ac	C ₂₄ H ₂₇ N ₃ O ₅
295727	(CH ₂) ₅ NHC(=NH)-N(CO ₂ CH ₂ Ph) ₂	cyclohexyl-CH ₂	Ph	C ₄₂ H ₅₂ N ₆ O ₈
295728	<i>t</i> -BuO	3-Pyr	Ph	C ₂₂ H ₂₆ N ₄ O ₅
295731	CH ₂ CH ₂ Ph	CH ₂ Ph	3-[(Ph) ₂ CH-OCO]-Ph	C ₄₂ H ₃₉ N ₃ O ₆

SOURCE – Naeja.

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1. Singh, R. et al. (Naeja Pharmaceuticals Inc.) *Substd. azetidin-2-ones as cysteine protease inhibitors*. WO 0059881.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

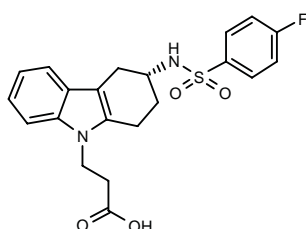
RAMATROBAN

Prop INN; BAN

137774

(+)-3-[3(*R*)-(4-Fluorophenylsulfonamido)-1,2,3,4-tetrahydrocarbazol-9-yl]propionic acid

Bay-u-3405⁺



C21 H21 F N2 O4 S; Mol wt: 416.4750

M.p. 134-5 °C, $[\alpha]_D^{+70.1^\circ}$ (c 1.0, MeOH).

ACTION – TxA₂ receptor antagonist.

INDICATION – Treatment of allergic rhinitis.

PRESENTATION – Tablets, 50 and 75 mg.

PROPRIETARY NAME – Baynas (JP).

SOURCE – Bayer.

RECENT REFERENCES

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2. Ishizuka, T. et al. *Novel TXA₂ receptor blockade, BAY u 3405, prevent MCP-1 expression, macrophage infiltration, and plaque instability in an atherosclerotic rabbit model*. J Am Coll Cardiol 2000, 35(2, Suppl. A): 253A.
3. Moriawaki, T. et al. *Comparison of pharmacokinetics of Bay u3405, and EHBR using a novel recirculation model in rats*. Xenobiotic Metab Dispos 1999, 14(Suppl.): Abst 20P15.
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5. Tanigawa, T. et al. *Population pharmacokinetics of ramatroban in healthy volunteers and patients with bronchial asthma/perennial allergic rhinitis*. Xenobiotic Metab Dispos 1997, 12(2): 121.
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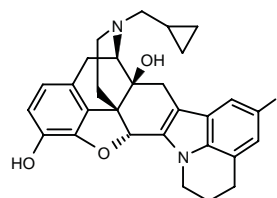
MONOGRAPH – Perzborn, E. et al. *Bay u 3405*. Drugs Fut 1991, 16(8): 0701.

*Drug Data Rep 1990, 012(03): 0210.

TRK-851

294488

(4b*S*,8*R*,8a*S*,16b*R*)-7-(Cyclopropylmethyl)-11-fluoro-5,6,7,8,9,14,15,16b-octahydro-4,8-methano-8a*H*,13*H*-[1]benzofuro[2,3-*a*]dipyrido[4,3-*b*:3',2',1'-*j**k*]carbazole-1,8a-diol



C29 H29 F N2 O3; Mol wt: 472.5571

ACTION – Selective opioid delta receptor antagonist with potent antitussive activity in rats and mice and fewer adverse reactions than the narcotic antitussive agents. Compound is expected to suppress cough associated with various acute and chronic respiratory diseases and is undergoing phase I clinical trials.

SOURCES – Mitsubishi-Tokyo Pharmaceuticals; Toray.

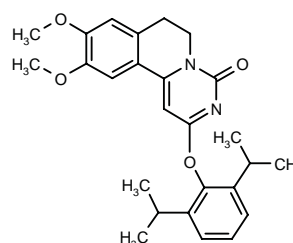
REFERENCES

1. Nagase, H. et al. (Toray Industries, Inc.) *Indole derivs. and medicinal use thereof*. EP 0805157, US 5849731, WO 9711948.
2. Maeda, M. et al. *Rational drug design and synthesis of opioid δ -receptor selective antagonist TRK-851 and its antitussive activity*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 1P-16.
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ASTHMA THERAPY

295381

2-(2,6-Diisopropylphenoxy)-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one



C26 H30 N2 O4; Mol wt: 434.5330

ACTION – Bronchodilating agent with phosphodiesterase type 3/4-inhibitory activity (IC_{50} = 107 and 1195 nM, respectively, against PDE3 and PDE4), potentially useful for the treatment of asthma and chronic obstructive pulmonary disease. The compound exhibits a longer duration of action and improved taste as compared to the known agent trequinsin. It was found to completely inhibit electrically stimulated guinea pig tracheal contractions with a long duration and to inhibit PHA-stimulated proliferation of human mononuclear cells (IC_{50} = 2.90 μ M). When tested in conscious guinea pigs via inhalation (25%, dry powder), compound provided significant protection against histamine-induced bronchospasm, without changing mean arterial blood pressure, whereas i.v. administration (0.1-300 μ g/kg) to anesthetized guinea pigs produced a dose-dependent reduction in mean arterial blood pressure. When administered orally at 10 mg/kg to ovalbumin-sensitized guinea pigs 1 h prior to antigen challenge, compound significantly inhibited eosinophil recruitment into the lungs.

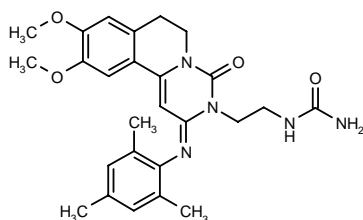
SOURCE – Vernalis.

REFERENCES

1. Oxford, A.W. and Jack, D. (Vernalis Ltd.) *Derivs. of pyrimido[6,1-a]isoquinolin-4-one*. WO 0058309.

295383

N-[2-[9,10-Dimethoxy-2-(2,4,6-trimethylphenylimino)-4-oxo-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-3-yl]ethyl]urea



C26 H31 N5 O4; Mol wt: 477.5619

ACTION – Agent for the treatment of respiratory disorders, particularly asthma, bronchitis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), allergic asthma, hay fever, allergic rhinitis and cystic fibrosis, as well as for the topical treatment of skin disorders such as atopic dermatitis and psoriasis and ocular inflammation, a representative compound from a series of pyrimido[6,1-*a*]isoquinolin-4-one derivatives with phosphodiesterase type 3/4-inhibitory activity and a longer duration of action and improved taste as compared to the known agent trequinsin. *In vitro*, compound exhibited IC_{50} values of 0.43 and 1479 nM against PDE3 and PDE4, respectively, and was found to completely inhibit electrically stimulated guinea pig tracheal contractions at 10 μ M, with a duration of effect of more than 2-4 h. It was also shown to inhibit the PHA-stimulated proliferation of human mononuclear cells (IC_{50} = 0.46 μ M) and lipopolysaccharide-induced release of TNF- α from human monocytes (IC_{50} = 7.5 nM). When tested *in vivo* via inhalation (2.5 and 25%, dry powder), compound provided significant protection against histamine-induced bronchospasm in conscious guinea pigs over 5.5 h and reduced mean blood pressure over this period. In addition, i.v. administration (1-100 μ g/kg) to

anesthetized guinea pigs produced a dose-dependent reduction in mean arterial blood pressure. When administered orally at 10 mg/kg to ovalbumin-sensitized guinea pigs 1 h prior to antigen challenge, compound significantly inhibited eosinophil recruitment into the lungs; exposure to dry powder (25%) 1.5 h prior to antigen challenge also significantly inhibited eosinophil recruitment into the lungs, with a duration of action of > 24 h.

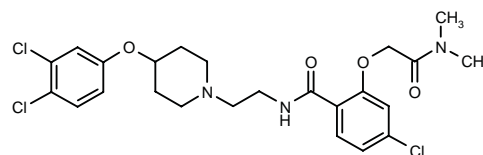
SOURCE – Vernalis.

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1. Oxford, A.W. and Jack, D. (Vernalis Ltd.) *Derivs. of pyrimido[6,1-a]isoquinolin-4-one*. WO 0058308.

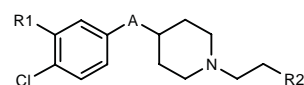
295415

4-Chloro-*N*-[2-[4-(3,4-dichlorophenoxy)piperidin-1-yl]ethyl]-2-[2-(dimethylamino)-2-oxoethoxy]benzamide



C24 H28 Cl3 N3 O4; Mol wt: 528.8612

ACTION – Chemokine receptor modulator, especially active at CCR1 and/or CCR3 receptors, potentially useful for the treatment of autoimmune, inflammatory, proliferative and immunologically mediated diseases. It is reported to antagonize the eotaxin-mediated calcium flux in human eosinophils and the MIP-1 α -mediated calcium flux in human monocytes. Other exemplified compounds include the following:



Compound	R1	R2	A	Formula
295416	Cl	2,4-(Cl)2-PhCONH	-O-	C ₂₀ H ₂₀ Cl ₄ N ₂ O ₂
295417	Cl	2-NH2-6-Me-4-pyrimidinyl-NH	-O-	C ₁₈ H ₂₃ Cl ₂ N ₅ O
295418	H	3-OH-4-MeO-PhCH2NH	-CO-	C ₂₂ H ₂₇ ClN ₂ O ₃
295419	Cl	3-MeO-PhCH2CONH	-O-	C ₂₂ H ₂₆ Cl ₂ N ₂ O ₃
295420	Cl	6-Me-2-Pyr-NHCH2	-O-	C ₂₀ H ₂₅ Cl ₂ N ₃ O

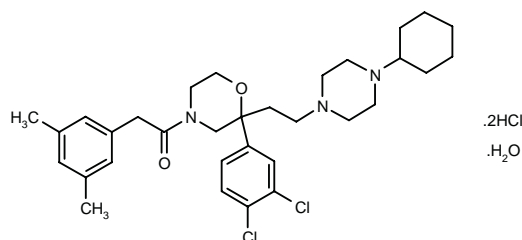
SOURCE – AstraZeneca.

REFERENCES

1. Baxter, A. et al. (AstraZeneca plc; AstraZeneca AB) *Novel cpds*. WO 0058305.

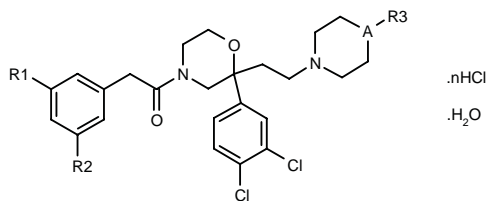
295430

(-)-1-[2-[2-(4-Cyclohexylpiperazin-1-yl)ethyl]-2-(3,4-dichlorophenyl)-4-morpholinyl]-2-(3,5-dimethylphenyl)-ethan-1-one dihydrochloride hydrate



C32 H43 Cl2 N3 O2 . 2HCl . H2O; Mol wt: 663.5533

ACTION – Agent with potent and selective affinity for tachykinin NK₁ receptors, potentially useful for the treatment of disorders associated with an excess of substance P and specifically claimed for chronic obstructive bronchitis, asthma, urinary incontinence, irritable bowel syndrome, Crohn's disease, ulcerative colitis, depression, anxiety and epilepsy. Other exemplified morpholine derivatives include the following:



Compound	R1=R2	R3	A	n	Formula
295431	Cl	cyclohexyl	N	2	C ₃₀ H ₃₇ Cl ₄ N ₃ O ₂ ·2HCl·H ₂ O
295432	CF ₃	cyclohexyl	N	2	C ₃₂ H ₃₇ Cl ₂ F ₆ N ₃ O ₂ ·2HCl·H ₂ O
295433	Me	C(Me)2CONH2	CH	1	C ₃₁ H ₄₁ Cl ₂ N ₃ O ₃ ·HCl·H ₂ O
295434	Et	C(Me)2CONH2	CH	1	C ₃₃ H ₄₅ Cl ₂ N ₃ O ₃ ·HCl·H ₂ O
295435	Cl	C(Me)2CONH2	CH	1	C ₂₉ H ₃₅ Cl ₄ N ₃ O ₃ ·HCl·H ₂ O

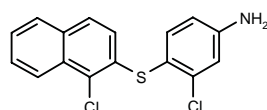
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Ducoux, J.P. et al. (Sanofi-Synthélabo) *Novel morpholine derivs., method for the production thereof and pharmaceutical preparations containing said derivs.* FR 2791346, WO 0058292.

295531

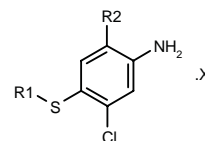
3-Chloro-4-(1-chloronaphthalen-2-ylsulfanyl)phenylamine



C16 H11 Cl2 N S; Mol wt: 320.2419

ACTION – A representative compound from a series of diaryl sulfides that bind to a novel regulatory site in the I domain of the leukocyte function-associated antigen (LFA-1) and thereby inhibit LFA-1 binding to ICAMs that bind LFA-1. *In vitro*, compound inhibited the adhesion of JY-8 cells (a human Epstein-Barr virus-transformed B-cell line expressing LFA-1 on its surface) to immobilized ICAM-1 and ICAM-3 with IC₅₀ values of 1.0 and 0.5 μM, respectively, in the absence of IL-8, and IC₅₀ values of 1.5 and 0.3 μM, respectively, in the presence of IL-8. Potentially useful for modulating leukocyte adhesion to

endothelial cells and in particular for the treatment of inflammatory and autoimmune diseases, as well as tumor metastasis, allograft rejection and reperfusion injury. Other exemplified compounds include the following:



Compound	R1	R2	X	Formula
295532	2,3-(Cl)2-Ph	H	HCl	C ₁₂ H ₈ Cl ₃ NS·HCl
295533	2,4-(Cl)2-Ph	H	HCl	C ₁₂ H ₈ Cl ₃ NS·HCl
295534	2,4-(Cl)2-Ph	Cl	HCl	C ₁₂ H ₇ Cl ₄ NS·HCl
295536	2-NO2-4-Cl-Ph	H		C ₁₂ H ₈ Cl ₂ N ₂ O ₂ S
295538	2,4-(Cl)2-Ph	H		C ₁₂ H ₈ Cl ₃ NS
295541	5-NO2-6-quinoliny	H		C ₁₅ H ₁₀ ClN ₃ O ₂ S
295542	2-benzothiazolyl	H		C ₁₃ H ₉ ClN ₂ S ₂

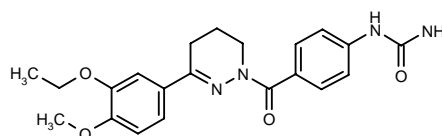
SOURCE – Icos.

REFERENCES

1. Fowler, K. et al. (Icos Corp.) *Inhibitors of LFA-1 binding to ICAMs and uses thereof.* WO 0059878.

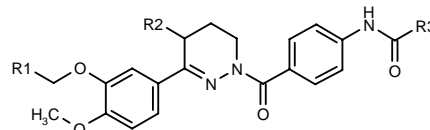
295680

N-[4-[3-(3-Ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazin-1-ylcarbonyl]phenyl]urea



C21 H24 N4 O4; Mol wt: 396.4446

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4) and TNF production, with potential for the treatment of allergies, asthma, osteoporosis, tumors, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, ulcerative colitis, inflammatory disorders, autoimmune diseases, AIDS, atopic dermatitis, psoriasis and transplant rejection. Other specifically claimed compounds from this series of tetrahydropyridazine derivatives are:



Compound	R1	R2	R3	Formula
295681	Et	H	3-Pyr	C ₂₇ H ₂₈ N ₄ O ₄
295682	Me	H	CF ₃	C ₂₂ H ₂₂ F ₃ N ₃ O ₄
295683	Et	H	OEt	C ₂₄ H ₂₉ N ₃ O ₅
295684	Me	H	i-PrO	C ₂₄ H ₂₉ N ₃ O ₅
295685	Me	H	OPr	C ₂₄ H ₂₉ N ₃ O ₅
295686	H	Et	3-Pyr	C ₂₇ H ₂₈ N ₄ O ₄
295687	H	Et	OEt	C ₂₄ H ₂₉ N ₃ O ₅
295688	H	Et	Me	C ₂₃ H ₂₇ N ₃ O ₄

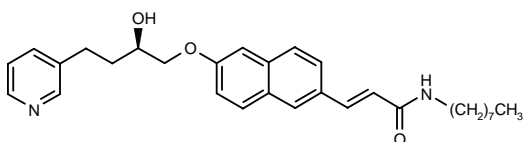
SOURCE – Merck KGaA.

REFERENCES

1. Rochus, J. et al. (Merck Patent GmbH) *Tetrahydropyridazine derivs.* DE 19915365, WO 0059890.

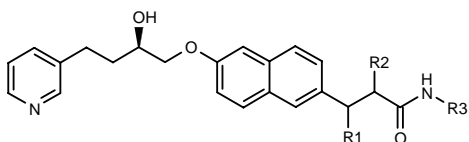
295798

3-[6-[2(*R*)-Hydroxy-4-(3-pyridinyl)butoxy]naphthalen-2-yl]-*N*-octyl-2(*E*)-propenamide



C₃₀ H₃₈ N₂ O₃; Mol wt: 474.6412

ACTION – Agent for the treatment or prevention of allergic, inflammatory, autoimmune, proliferative and hyperproliferative disorders, particularly asthma and rhinitis, that acts by inhibiting the activation of cell types of hematopoietic lineage such as mast cells, neutrophils and eosinophils. Within this series of pyridine derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
295799	H	H	C ₈ H ₁₇	C ₃₀ H ₄₀ N ₂ O ₃
295800	bond		Ph	C ₂₈ H ₂₆ N ₂ O ₃
295801	H	H	Ph	C ₂₈ H ₂₈ N ₂ O ₃
295803	H	H	(CH ₂) ₄ Ph	C ₃₂ H ₃₆ N ₂ O ₃
295804	H	H	cyclohexyl	C ₂₈ H ₃₄ N ₂ O ₃
295806	H	H	4-morpholinyl-(CH ₂) ₃	C ₂₉ H ₃₇ N ₃ O ₄
295807	H	H	t-BuOCONH(CH ₂) ₁₀	C ₃₇ H ₅₃ N ₃ O ₅

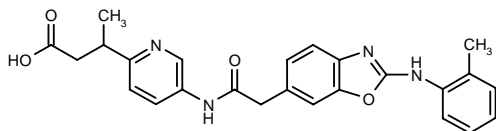
SOURCE – AstraZeneca.

REFERENCES

1. Andersson, M. et al. (AstraZeneca AB) *Novel cpds.* WO 0061560.

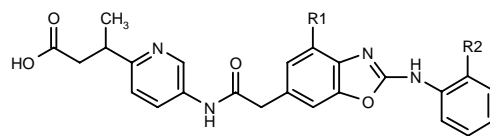
296012

3-[5-[2-[2-(2-Methylphenylamino)benzoxazol-6-yl]acetamido]pyridin-2-yl]butyric acid

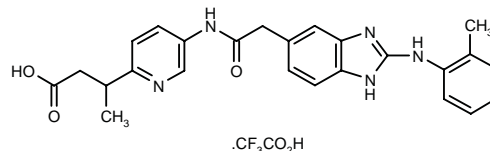


C₂₅ H₂₄ N₄ O₄; Mol wt: 444.4886

ACTION – Antiinflammatory agent with the ability to regulate the interaction of VCAM-1 and fibronectin with the $\alpha_4\beta_1$ integrin, particularly useful for the treatment of asthma. Other exemplified substituted bicyclic heteroaryl compounds include the following:



Compound	R1=R2	Formula
296014	Me	C ₂₆ H ₂₆ N ₄ O ₄
296015	H	C ₂₄ H ₂₂ N ₄ O ₄



296013: C₂₅ H₂₅ N₅ O₃ . C₂ H F₃ O₂

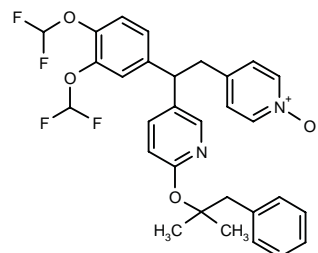
SOURCE – Aventis Pharma.

REFERENCES

1. Clark, D.E. et al. (Aventis Pharma Ltd.) *Substd. bicyclic heteroaryl cpds. as integrin antagonists.* WO 0061580.

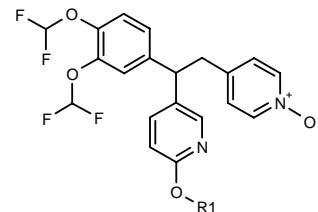
296550

4-[2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1,1-dimethyl-2-phenylethoxy)pyridin-3-yl]ethyl]pyridine *N*-oxide



C₃₀ H₂₈ F₄ N₂ O₄; Mol wt: 556.5532

ACTION – Selective phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 0.2 nM against human recombinant PDE4a-mediated hydrolysis of cAMP) with potential in the prophylaxis and treatment of asthma and other inflammatory conditions. Compound is reported to have good oral activity and exhibit little or none of the side effects associated with known PDE4 inhibitors such as rolapram. Other compounds from this series of hetero-substituted pyridine derivatives include the following:



Compound	R1	Formula
296551	4-(CF ₃ O)-Ph	C ₂₇ H ₁₉ F ₇ N ₂ O ₅
296552	3,4-(F)2-PhCH ₂	C ₂₇ H ₂₀ F ₆ N ₂ O ₄
296553	4-F-PhC(Me) ₂ CH ₂	C ₃₀ H ₂₇ F ₃ N ₂ O ₄

SOURCE – Merck Frosst.

REFERENCES

1. Frenette, R. et al. (Merck Frosst Canada Inc.) *Heterosubst. pyridine derivs. as PDE 4 inhibitors*. US 6180650, WO 0064874.

BUDESONIDE/FORMOTEROL FUMARATE

New combination

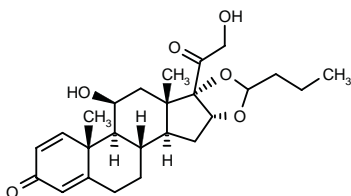
284152

Combination of budesonide and formoterol fumarate in a single inhaler

Budesonide

091057

(11 β ,16 α)-16,17-[Butylidenebis(oxy)]-11,21-dihydroxy-pregna-1,4-dione

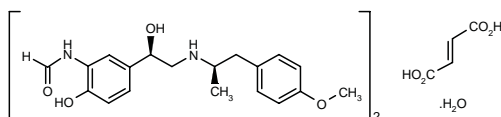


C25 H34 O6 ; Mol wt: 430.5376

Formoterol fumarate

125563

(\pm)-*N*-[2-Hydroxy-5-[1(*R**)-hydroxy-2-[1(*R**)-methyl-2-(4-methoxyphenyl)ethylamino]ethyl]phenyl]formamide fumarate (2:1) monohydrate



2(C19 H24 N2 O4) . C4 H4 O4 . H2O ; Mol wt: 822.9036

ACTION – Antiasthmatic combination of the rapid- and long-acting bronchodilating β_2 -adrenoceptor agonist formoterol and the antiinflammatory corticosteroid budesonide.

INDICATION – Treatment of asthma where use of both an inhaled corticosteroid and long-acting β_2 -agonist is appropriate, i.e., patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short-acting β_2 -agonists, or patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 -agonists.

PRESENTATION – Dry powder inhaler, 160 μ g budesonide plus 4.5 μ g formoterol fumarate per inhalation and 80 μ g budesonide plus 4.5 μ g formoterol fumarate per inhalation.

PROPRIETARY NAME – Symbicort Turbuhaler (SE).

SOURCE – AstraZeneca.

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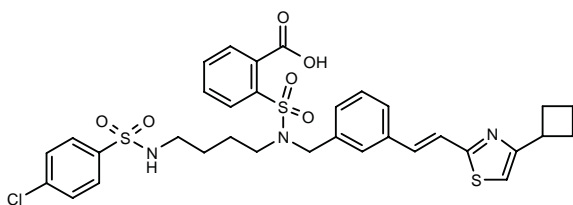
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S-36496

296926

(E)-2-[N-[4-(4-Chlorophenylsulfonamido)butyl]-N-[3-[2-(4-cyclobutylthiazol-2-yl)ethenyl]benzyl]sulfamoyl]benzoic acid



C33 H34 Cl N3 O6 S3; Mol wt: 700.2976

ACTION – Dual LTD₄ and TxA₂ receptor antagonist (pA₂ = 9.73 and 8.69, respectively, in guinea pig tracheal smooth muscle), proven to reverse the increase in guinea pig airways resistance induced by LTD₄ and U-46619. In sensitized guinea pigs, compound given by inhalation as a 0.1% solution significantly inhibited antigen-induced immediate and late asthmatic reactions, as well as airways hypersensitivity. In addition, compound given as a powder for inhalation (300 µg) inhibited bronchoconstriction induced by LTD₄, U-46619 or passive sensitization in guinea pigs; this effect was sustained and it inhibited contractions even when antigen challenge was performed 6 h after administration. Although it had no effect on antigen-induced eosinophilia in bronchoalveolar lavage fluid of guinea pigs, it inhibited eosinophil infiltration into airways tissue and mucus production following inhalation of a 0.1% solution. Potentially useful for the treatment of asthma.

SOURCE – Kaken.

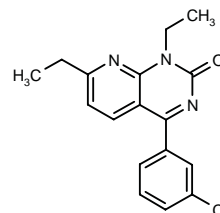
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YM-976*

252426

4-(3-Chlorophenyl)-1,7-diethylpyrido[2,3-d]pyrimidin-2(1H)-one



C17 H16 Cl N3 O; Mol wt: 313.7864

ACTION – Potent, selective and competitive inhibitor of phosphodiesterase type 4 (PDE4) giving an IC₅₀ value of 2.2 nM (in human peripheral leukocytes) compared to respective values of 820 and 0.43 nM for rolipram and RP-73401; it was inactive against other PDE isozymes and was found to inhibit TNF-α production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells (IC₅₀ = 9.4 nM) more potently than rolipram (IC₅₀ = 76 nM), but less so than RP-73401 (IC₅₀ = 0.82 nM). In the carrageenan-induced pleurisy model in rats, it inhibited cell infiltration with an oral ED₃₀ value of 9.1 mg/kg vs. 10 and 7.4 mg/kg for rolipram and RP-73401, respectively. In models of antigen-induced eosinophil accumulation in the lungs in sensitized mice, rats and ferrets, compound dose-dependently inhibited eosinophilia with respective ED₅₀ values of 3.6, 1.7 and 1.2 mg/kg p.o. In mice, the compound also inhibited IL-5 production with an ED₅₀ of 5.8 mg/kg p.o. In a model of eosinophilia induced by repeated exposure to antigen in rats, chronic administration of compound was more effective than single doses, with ED₅₀ values of 0.32 mg/kg p.o. and 1.4 mg/kg p.o., respectively. Unlike rolipram and RP-73401, it was devoid of emetic effect in ferrets at up to 10 mg/kg p.o. Potentially useful for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

SOURCE – Yamanouchi.

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*Identified compound **252426** Drug Data Rep 1998, 020(05): 0394.

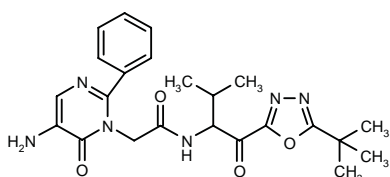
TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

ONO-6818

285811

2-(5-Amino-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl)-*N*-[1-(5-*tert*-butyl-1,3,4-oxadiazol-2-ylcarbonyl)-2-methylpropyl]acetamide

Ono-PO-736



C23 H28 N6 O4; Mol wt: 452.5122

ACTION – Highly selective, orally active, reversible, nonpeptide inhibitor of human neutrophil elastase (HNE; $K_i = 12.16$ nM) proven to produce long-lasting (> 8 h) inhibition of HNE-induced lung hemorrhage in hamsters when given as a suspension in carboxymethyl cellulose ($ED_{50} = 1.4$ mg/kg p.o.). Compound showed good oral bioavailability in rats (51%), dogs (31%) and monkeys (18%). In sensitized guinea pigs, a dose of 100 mg/kg p.o. prior to antigen challenge inhibited mucus secretion in goblet cells, with no effect on inflammatory cell infiltration into the airways mucosa. Currently undergoing phase I clinical studies as a potential treatment for chronic obstructive pulmonary disease (COPD).

SOURCES – Cortech; Ono.

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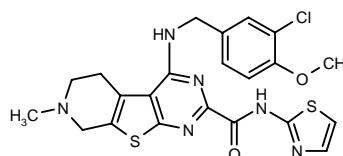
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- Kojima, T. et al. (Ono Pharmaceutical Co., Ltd.) *Pyrimidine derivs, process for preparing the derivs. and drugs containing the same as active ingredient*. WO 0123361.
- Nakada, J. et al. *Effects of ONO 6818 to antigen challenge-induced secretory promotion in goblet cell*. Jpn J Allergol 2000, 49(9-10): Abst 272.
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- New treatment for COPD from Ono to enter clinical trials soon*. DailyDrugNews.com (Daily Essentials) 2000, Feb 24.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

295587

4-(3-Chloro-4-methoxybenzylamino)-7-methyl-*N*-(2-thiazolyl)-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine-2-carboxamide



C22 H21 Cl N6 O2 S2; Mol wt: 501.0329

ACTION – cGMP-specific phosphodiesterase inhibitor, particularly active against PDE5, with an IC_{50} of 0.55 nM against recombinant human PDE5 and high selectivity over other isoforms ($IC_{50} > 10,000$ nM for inhibition of PDE1, PDE2, PDE3 and PDE4). The compound antagonized phenylephrine-induced contractions in rat thoracic aorta preparations ($EC_{50} = 2.7$ nM). Potentially useful for the treatment of hypertension, heart failure, myocardial infarction, angina pectoris, arteriosclerosis, post-PTCA restenosis, pulmonary hypertension, renal failure, renal edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, glaucoma and male erectile dysfunction.

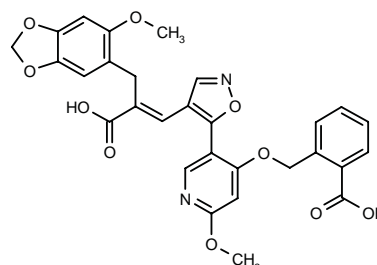
SOURCE – Nippon Soda.

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295712

2-[5-[4-[2-Carboxy-3-(6-methoxy-1,3-benzodioxol-5-yl)-1(*E*)-propenyl]isoxazol-5-yl]-2-methoxypyridin-4-yloxy-methyl]benzoic acid



C29 H24 N2 O10; Mol wt: 560.5126

ACTION – Endothelin receptor antagonist for the treatment of renal failure, hypertension, pulmonary hypertension and heart failure. Other specifically claimed compounds are:

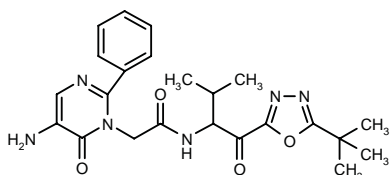
TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

ONO-6818

285811

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Ono-PO-736



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SOURCES – Cortech; Ono.

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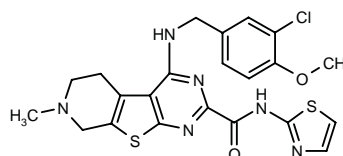
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- Ohmoto, K. et al. *Design and synthesis of new orally active nonpeptide inhibitors of human neutrophil elastase*. J Med Chem 2000, 43(26): 4927.
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- New treatment for COPD from Ono to enter clinical trials soon*. DailyDrugNews.com (Daily Essentials) 2000, Feb 24.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

295587

4-(3-Chloro-4-methoxybenzylamino)-7-methyl-*N*-(2-thiazolyl)-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine-2-carboxamide



C22 H21 Cl N6 O2 S2; Mol wt: 501.0329

ACTION – cGMP-specific phosphodiesterase inhibitor, particularly active against PDE5, with an IC_{50} of 0.55 nM against recombinant human PDE5 and high selectivity over other isoforms ($IC_{50} > 10,000$ nM for inhibition of PDE1, PDE2, PDE3 and PDE4). The compound antagonized phenylephrine-induced contractions in rat thoracic aorta preparations ($EC_{50} = 2.7$ nM). Potentially useful for the treatment of hypertension, heart failure, myocardial infarction, angina pectoris, arteriosclerosis, post-PTCA restenosis, pulmonary hypertension, renal failure, renal edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, glaucoma and male erectile dysfunction.

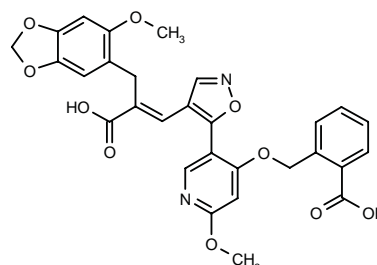
SOURCE – Nippon Soda.

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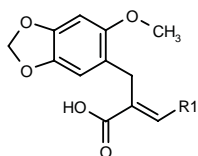
295712

2-[5-[4-[2-Carboxy-3-(6-methoxy-1,3-benzodioxol-5-yl)-1(*E*)-propenyl]isoxazol-5-yl]-2-methoxypyridin-4-yloxy-methyl]benzoic acid

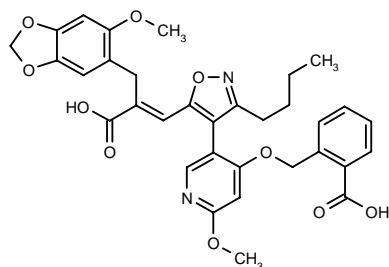


C29 H24 N2 O10; Mol wt: 560.5126

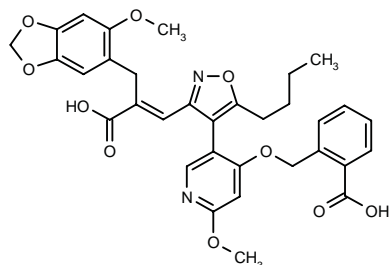
ACTION – Endothelin receptor antagonist for the treatment of renal failure, hypertension, pulmonary hypertension and heart failure. Other specifically claimed compounds are:



Compound	R1	Formula
295715	5-(3-CO ₂ H-5-Cl-2-thienyl)-4-isoxazolyl	C ₂₀ H ₁₄ ClNO ₆ S
295716	3-[6-MeO-4-(2-CO ₂ H-PhCH ₂ O)-3-Pyr]-4-isoxazolyl	C ₂₉ H ₂₄ N ₂ O ₁₀
295717	3-(3-CO ₂ H-5-Cl-2-thienyl)-4-isoxazolyl	C ₂₀ H ₁₄ ClNO ₆ S



295718: C33 H32 N2 O10



295720: C33 H32 N2 O10

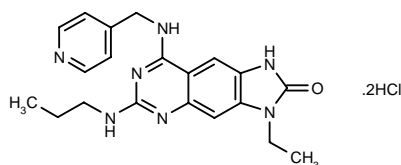
SOURCE – GlaxoSmithKline.

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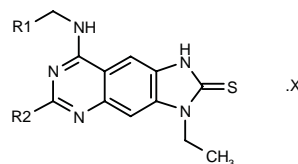
296595

3-Ethyl-6-(propylamino)-8-(4-pyridinylmethylamino)-2,3-dihydro-1*H*-imidazo[4,5-*g*]quinazolin-2-one dihydrochloride



C₂₀ H₂₃ N₇ O . 2HCl; Mol wt: 450.3715

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor with potential in the treatment of cardiovascular disorders such as angina pectoris, hypertension, heart failure, arteriosclerosis, restenosis following PTCA and thrombosis, as well as asthma and allergic disorders, gastrointestinal disorders such as irritable bowel syndrome, glaucoma and impotence. Compound exhibited potent antihypertensive activity in rats following intraduodenal administration of 10 mg/kg. Other compounds from this series of imidazoquinazoline derivatives include the following:



Compound	R1	R2	X	Formula
296596	4-Pyr	NHPr	2HCl	C ₂₀ H ₂₃ N ₇ S.2HCl
296598	1,3-benzodioxol-5-yl	4-CO ₂ H-1-Pip		C ₂₅ H ₂₆ N ₆ O ₄ S
296599	2-[4-(CH ₂ OH)-1-Pip]-Ph	OMe		C ₂₅ H ₃₀ N ₆ O ₂ S
296601	2-[4-(CH ₂ OH)-1-Pip]-Ph	SMe		C ₂₅ H ₃₀ N ₆ OS ₂
296602	2-[4-(CH ₂ OH)-1-Pip]-Ph	SEt		C ₂₆ H ₃₂ N ₆ OS ₂
296604	2-[4-(CH ₂ OH)-1-Pip]-Ph	1-imidazolyl		C ₂₇ H ₃₀ N ₈ OS
296605	2-[4-(CH ₂ OH)-1-Pip]-Ph	4-morpholinyl		C ₂₈ H ₃₅ N ₇ O ₂ S

SOURCE – Kyowa Hakko.

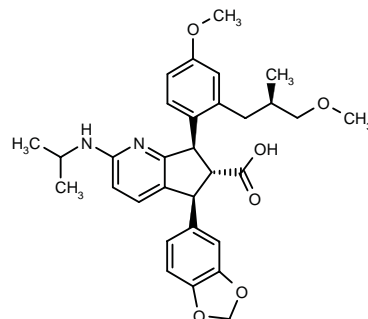
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J-105859

298790

(+)-(5*S*,6*R*,7*R*)-5-(1,3-Benzodioxol-5-yl)-2-(isopropylamino)-7-[2-[2(*R*)-methyl-3-methoxypropyl]-4-methoxyphenyl]-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-6-carboxylic acid



C₃₁ H₃₆ N₂ O₆; Mol wt: 532.6334

ACTION – Selective endothelin ET_A receptor antagonist ($K_i = 0.025$ and 48 nM for binding affinity to human cloned ET_A and ET_B receptors, respectively) able to selectively inhibit ET-1-induced contractions in rabbit iliac artery ($pA_2 = 10.08$) while being less effective against ET_B agonist-induced rabbit pulmonary artery contractions ($pA_2 = 7.63$). *In vivo*, compound exhibited significant activity in inhibiting the pressor response to i.v. ET-1 in rats, providing over 50% inhibition at 0.1 mg/kg i.v. In salt-loaded Dahl salt-sensitive rats, chronic treatment with compound (0.1 and 1 mg/kg/day p.o., starting before the development of hypertension) significantly reduced mortality, increasing the survival rate from 34% in controls to 80% on 0.1 mg/kg/day and 100% on 1 mg/kg/day. Moreover, compound at the dose of 1 mg/kg markedly attenuated the development of hypertension and prevented the development of brain lesions.

SOURCE – Banyu.

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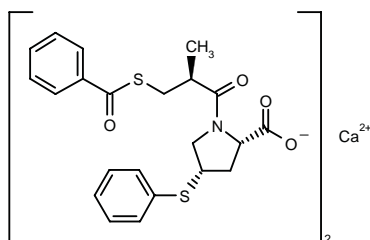
ZOFENOPRIL+ CALCIUM

Rec INN; BANM; USAN

90826

(4S)-N-[3-(Benzoylsulfanyl)-2(S)-methylpropionyl]-4-(phenylsulfanyl)-L-proline calcium salt

SQ-26991



C44 H44 Ca N2 O8 S2; Mol wt: 897.1796

ACTION – Prodrug that releases the active angiotensin-converting enzyme (ACE) inhibitor zofenoprilat⁺⁺ via thio ester hydrolysis.

INDICATION – Treatment of mild to moderate essential hypertension and acute myocardial infarction.

PRESENTATION – Tablets, 15 and 30 mg.

PROPRIETARY NAMES AND SOURCES – *Bifril* (Menarini, IT); *Zantipres* (F.I.R.M.A., IT); *Zofepiril* (Menarini, IT); *Zopranol* (Guidotti, IT).

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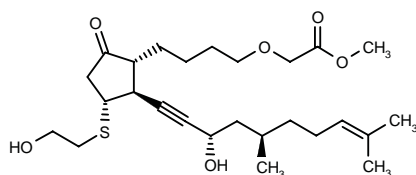
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**Drug Data Rep 1991, 013(01): 0028.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

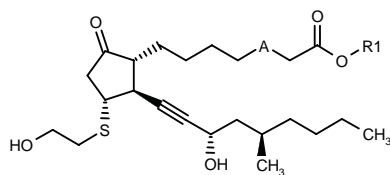
296016

11-Deoxy-11(*R*)-(2-hydroxyethylsulfanyl)-20-isopropylidene-17(*R*)-methyl-13,14-didehydro-3-oxaprostaglandin E₁ methyl ester



C26 H42 O6 S; Mol wt: 482.6778

ACTION – Prostaglandin E₁ derivative that inhibits vascular smooth muscle proliferation, as demonstrated in human aorta-derived vascular cells. Potentially useful for the treatment of vascular hypertrophy and obstruction, and for preventing post-PTCA restenosis. Other exemplified compounds include the following:



Compound	R1	A	Formula
296017	H	CH2	C ₂₄ H ₄₀ O ₅ S
296018	Me	O	C ₂₄ H ₄₀ O ₆ S

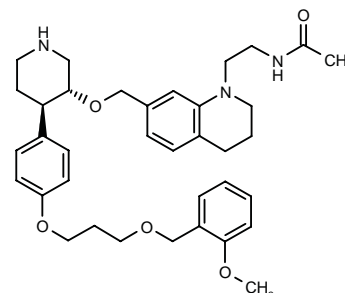
SOURCE – Taisho.

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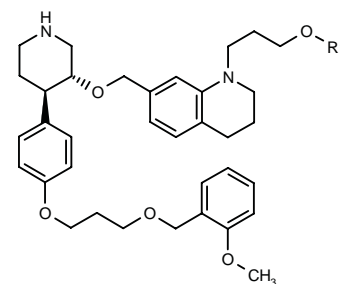
296460

N-[2-[7-[4(*R*)-[4-[3-(2-Methoxybenzyloxy)propoxy]-phenyl]piperidin-3(*R*)-yloxymethyl]-1,2,3,4-tetrahydroquinolin-1-yl]ethyl]acetamide



C36 H47 N3 O5; Mol wt: 601.7833

ACTION – Human renin inhibitor (IC₅₀ = 0.05 nM) that is useful for the treatment of disorders associated with restenosis, glaucoma, cardiac infarction, hypertension and end organ damage, such as cardiac or renal insufficiency. Other specifically claimed piperidine derivatives are:



Compound	R1	Formula
296461	H	C ₃₅ H ₄₆ N ₂ O ₅
296462	Me	C ₃₆ H ₄₈ N ₂ O ₅

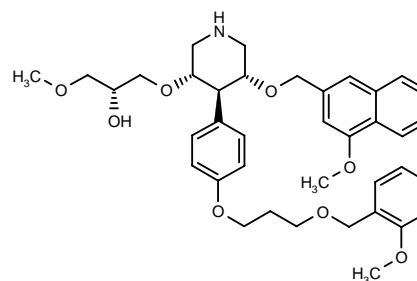
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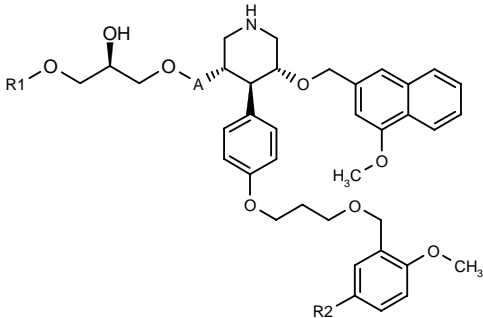
296463

1-Methoxy-3-[4(*R*)-[4-[3-(2-methoxybenzyloxy)propoxy]-phenyl]-5(*R*)-(4-methoxynaphthalen-2-ylmethoxy)-piperidin-3(*S*)-yloxy]propan-2(*R*)-ol



C38 H47 N O8; Mol wt: 645.7883

ACTION – Human renin inhibitor (IC₅₀ = 0.06 nM) potentially useful for the treatment of disorders associated with restenosis, glaucoma, cardiac infarction, hypertension and end organ damage such as cardiac or renal insufficiency. Other specifically claimed piperidine derivatives are:



Compound	R1	R2	A	Formula
296464	H	H	CH2	C ₃₈ H ₄₇ NO ₈
296465	H	F	bond	C ₃₇ H ₄₄ FNO ₈
296466	Me	F	bond	C ₃₈ H ₄₆ FNO ₈
296467	Me	H	CH2	C ₃₉ H ₄₉ NO ₈

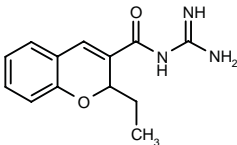
SOURCE – Roche.

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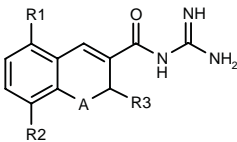
296579

N-(2-Ethyl-2H-1-benzopyran-3-ylcarbonyl)guanidine



C13 H15 N3 O2; Mol wt: 245.2805

ACTION – Na⁺/H⁺ exchange (NHE) inhibitor, potentially useful as an antianginal, antiischemic and cardioprotective agent, as well as for the treatment of peripheral vascular disorders including intermittent claudication. Other specifically claimed compounds from this series of bicyclic acyl guanidine derivatives include the following:



Compound	R1	R2	R3	A	Formula
296580	H	H	Me	S	C ₁₂ H ₁₃ N ₃ OS
296581	Cl	H	Me	O	C ₁₂ H ₁₂ ClN ₃ O ₂
296582	H	Cl	(R)-Me	O	C ₁₂ H ₁₂ ClN ₃ O ₂
296583	OMe	H	CF3	O	C ₁₃ H ₁₂ F ₃ N ₃ O ₃
296584	H	Me	(R)-CF3	O	C ₁₃ H ₁₂ F ₃ N ₃ O ₂
296585	Cl	H	(R)-CF3	O	C ₁₂ H ₉ ClF ₃ N ₃ O ₂

SOURCE – Bristol-Myers Squibb.

REFERENCES

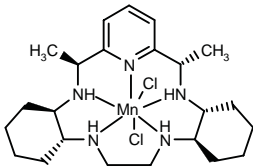
1. Dugar, S. and O'Neil, S.V. (Bristol-Myers Squibb Co.) *Bicyclic acyl guanidine sodium/proton exchange inhibitors and method*. WO 0064445.

M-40401

298882

(PB-7-11-2344'3')-Dichloro[(4aR,6S,12S,13aR,17aR,21aR)-6,12-dimethyl-11,7-nitrilo-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-eicosahydro-7H-dibenzo[b,h][1,4,7,10]tetraazacycloheptadecine-κN⁵,κN¹³,κN¹⁸,κN²¹,κN²²]manganese

SC-73770



C23 H39 Cl2 Mn N5; Mol wt: 511.4401

ACTION – Superoxide dismutase (SOD) mimetic, a derivative of M-40403 with much higher catalytic activity and proven to be effective in a rat model of splanchnic artery occlusion (SAO) shock. Compound given at doses of 0.25-25 μg/kg i.v. 15 min before reperfusion was found to attenuate the decrease in mean arterial blood pressure, neutrophil infiltration into the ileum and lung, and the increase in plasma and ileum levels of malondialdehyde, TNF-α and IL-1β. In addition, it also significantly increased the survival rate from 0% in vehicle-treated controls to 100% 4 h after reperfusion. Immunohistochemical studies showed marked reductions in nitrotyrosine, P-selectin and ICAM-1 staining in ileum of shocked rats dosed with compound. Potentially useful in ischemia–reperfusion injury.

SOURCES – MetaPhore; Pharmacia.

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RAMIPRIL +

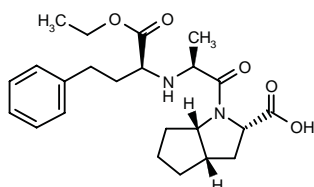
Rec INN; BAN; USAN

New indication**090507**

(2*S*,3*aS*,6*aS*)-1-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid

1-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-1(*S*,5*S*)-2-azabicyclo[3.3.0]octane-3(*S*)-carboxylic acid

Hoe-498



C23 H32 N2 O5; Mol wt: 416.5220

ACTION – Prodrug of the active angiotensin-converting enzyme (ACE) inhibitor ramiprilat⁺⁺ that is converted to the latter via hepatic cleavage of the ester group, first approved for the treatment of hypertension and subsequently for the treatment of congestive heart failure after a heart attack.

INDICATION – Reduction of the risk of myocardial infarction, stroke and death from cardiovascular causes in patients 55 and over either with a history of coronary artery disease, stroke or peripheral vascular disease, or with diabetes and one other cardiovascular risk factor.

PRESENTATION – Capsules, 1.25, 2.5, 5 and 10 mg.

PROPRIETARY NAME – *Altace* (US).

SOURCES – Aventis; marketed in the US by Monarch Pharmaceuticals, a subsidiary of King Pharmaceuticals.

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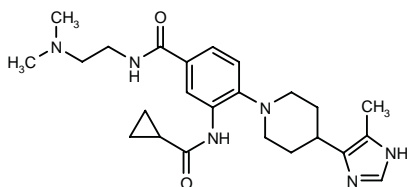
*Drug Data Rep 1990, 012(03): 0203.

**Drug Data Rep 1985, 007(09): 0579.

SL-59.1227*

271820

3-(Cyclopropylcarboxamido)-N-[2-(dimethylamino)ethyl]-4-[4-(5-methyl-1H-imidazol-4-yl)piperidin-1-yl]benzamide



C₂₄ H₃₄ N₆ O₂; Mol wt: 438.5726

ACTION – Cardioprotective agent, an Na⁺/H⁺ exchange (NHE) inhibitor shown to selectively inhibit the cardiac NHE-1 isoform versus the epithelial NHE-2 isoform (IC₅₀ = 3.3 nM and 2.3 μM, respectively), being about 30-fold more potent than the acylguanidine inhibitor cariporide (IC₅₀ = 103 nM and 73 μM, respectively). In anesthetized rats subjected to coronary artery occlusion followed by reperfusion, compound infused before ischemia at doses of 10-100 μg/kg/min was shown to dose-dependently inhibit ventricular tachycardia during ischemia (71-100%) and ventricular fibrillation during reperfusion (75-87%), and to prevent mortality. In the same model, significant antiarrhythmic effects and protection against mortality were also seen after an i.v. bolus of 1 mg/kg either prior to or during ischemia. In rabbits following left coronary artery occlusion and reperfusion, compound significantly reduced cardiac infarct size measured as percentage of the area at risk (54% reduction at 0.6 mg/kg i.v.).

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Cremer, G. et al. (Sanofi-Synthélabo) *4-[(1H-imidazol-4-yl)piperidin-1-yl]anilide derivs., their preparation and application in therapy*. EP 0991639, WO 9900379.

2. Lorrain, J. et al. *Pharmacological profile of SL 59.1227, a novel inhibitor of the sodium/hydrogen exchanger*. Br J Pharmacol 2000, 131(6): 1188.

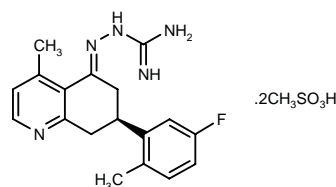
*Identified compound **271820** (see **271815**) Drug Data Rep 1999, 021(02): 0134.

T-559

296942

2(E)-[7(S)-(5-Fluoro-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydroquinolin-5-ylidene]hydrazinecarboxamide dimethanesulfonate

T-162559



C₁₈ H₂₀ F N₅ . 2 C H₄ O₃ S; Mol wt: 517.6002

ACTION – Nonacylguanidine Na⁺/H⁺ exchange (NHE) inhibitor with an IC₅₀ value of 15 nM for NHE in rat platelets. In a model of myocardial infarction in rats, compound (0.1 mg/kg) given i.v. 5 min or 2 h prior to coronary artery occlusion (1 h) followed by reperfusion (24 h) showed potent and long-lasting cardioprotective effects.

SOURCE – Takeda.

REFERENCES

1. Shiraishi, M. et al. (Takeda Chemical Industries, Ltd.) *Aminoguanidine hydrazone derivs., process for producing the same and drugs thereof*. EP 1057812, JP 2000191641, WO 9942442.

2. Fukumoto, S. et al. *Novel, non-acylguanidine type Na⁺/H⁺ exchanger inhibitors: Synthesis and biological evaluation of tetrahydroquinolinydene aminoguanidine derivatives*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 2P-02.

3. Igata, H. et al. *Potent and long-lasting cardioprotective effects of T-162559, a new Na-H exchange inhibitor, in rats*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-73.

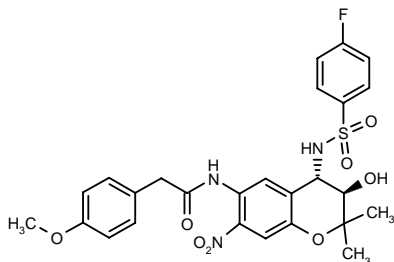
4. Kusumoto, K. et al. *In vitro and in vivo pharmacology of a new Na-H exchange inhibitor, T-162559*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-68.

5. Nishimura, S. et al. *Effects of T-162559, a new Na-H exchange inhibitor, on myocardial infarct size and release of cardiac proteins in coronary artery occlusion-reperfusion dogs*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-71.

ANTIARRHYTHMIC DRUGS

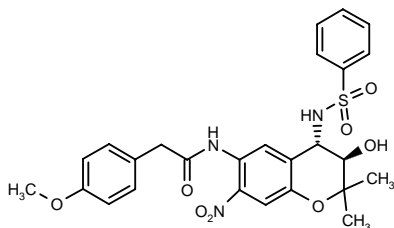
295468

N-[4(*S*)-(4-Fluorophenyl)sulfonamido)-3(*R*)-hydroxy-2,2-dimethyl-7-nitro-3,4-dihydro-2*H*-1-benzopyran-6-yl]-2-(4-methoxyphenyl)acetamide



C₂₆ H₂₆ F N₃ O₈ S; Mol wt: 559.5684

ACTION – Antiarrhythmic agent that selectively prolongs atrial refractory period, as demonstrated in guinea pig left atrial muscle preparations, where compound produced 33% prolongation of the refractory period at 10 μ M. Another compound from this series of chroman derivatives is:



295469: C₂₆ H₂₇ N₃ O₈ S

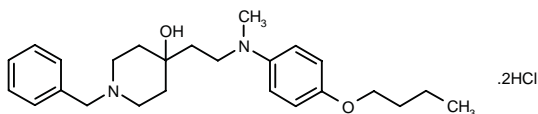
SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Chroman derivs.* JP 2000336085, WO 0058300.

296072

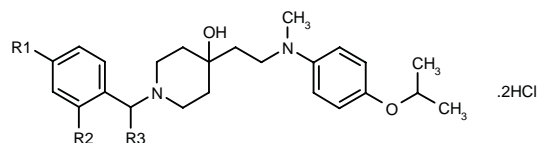
1-Benzyl-4-[2-[*N*-(4-butoxyphenyl)-*N*-methylamino]ethyl]piperidin-4-ol dihydrochloride



C₂₅ H₃₆ N₂ O₂ · 2HCl; Mol wt: 469.4932

ACTION – Antiarrhythmic agent proven to inhibit veratrine-induced contractions of isolated rat cardiac muscle with an IC₅₀ value of 1.2 μ M. *In vivo*, compound dose-dependently (5-20 mg/kg p.o.) inhibited ischemia/reperfusion-induced ventricular fibrillation in rats, providing complete inhibition at 20 mg/kg p.o. It also inhibited the appearance of arrhythmias in dogs following coronary artery ligation at 10 mg/kg/h i.v., while being devoid of

effects on P-Q and QRS intervals in rats at 5 mg/kg i.v. No mortality or signs of toxicity were observed following administration of 100 mg/kg/day p.o. for 2 weeks. Other compounds from this series of 4-hydroxypiperidine derivatives include the following:



Compound	R1	R2	R3	Formula
296688	CO ₂ Me	H	H	C ₂₆ H ₃₆ N ₂ O ₄ ·2HCl
296691	Br	F	H	C ₂₄ H ₃₂ BrFN ₂ O ₂ ·2HCl
296693	H	H	Ph	C ₃₀ H ₃₈ N ₂ O ₂ ·2HCl

SOURCE – Mochida.

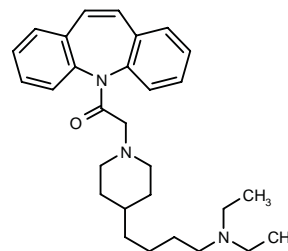
REFERENCES

1. Yamamoto, I. et al. (Mochida Pharmaceutical Co., Ltd.) *4-Hydroxypiperidine derivs. having antiarrhythmic effect.* WO 0061557.

MF-10058

295582

5-[2-[4-[4-(Diethylamino)butyl]piperidin-1-yl]acetyl]-5*H*-dibenzo[*b,f*]azepine



C₂₉ H₃₉ N₃ O; Mol wt: 445.6471

ACTION – High-affinity ligand for human muscarinic M₂ receptors (K_i = 2.6 nM) with 39-, 119- and 112-fold lower affinity for M₄, M₁ and M₃ receptors, respectively. In an *in vitro* functional assay, compound showed competitive and selective M₂-antagonist activity, with a pA₂ value of 7.08 for antagonism of the methacholine-induced decrease in the contractile response to field stimulation in guinea pig left atria. In rats, compound was found to antagonize acetylcholine-induced bradycardia and hypotension, with respective ED₅₀ values of 55 and 80 μ g/kg i.v. Compound given i.d. or p.o. significantly reduced nocturnal bradycardia in dogs and at the highest dose of 10 mg/kg this effect lasted for 24 h. No M₁ or M₃ receptor-mediated responses were seen in rats (oxotremorine-stimulated salivary secretion, gastric emptying, pupil diameter, etc.) at doses up to 30 times higher than the antibradycardic dose. Moreover, the lack of analgesic effect in mice indicated poor blood-brain barrier penetration. Potentially useful for the treatment of cardiac conduction dysfunction, i.e., sinus or nodal bradycardia (sick sinus syndrome) and atrioventricular block.

SOURCE – Mediolanum.

REFERENCES

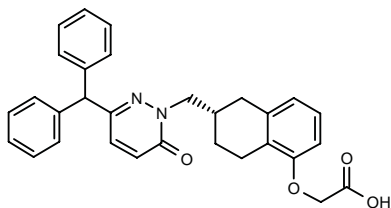
1. Terni, P.M.L. et al. (Mediolanum Farmaceutici) *Selective M2 muscarinic receptor antagonists having 5H-dibenz[b,f]azepine structure*. WO 0102386.
2. Lamperti, G. et al. *Hemodynamic effects of MF 10058, a new cardioselective muscarinic M-2 receptor antagonist, in conscious dogs*. Eur J Pharmacol 2000, 406(1): 93.
3. Mandelli, G.R. et al. *Synthesis of new cardioselective M2 muscarinic receptor antagonists*. Chem Pharm Bull 2000, 48(11): 1611.

TREATMENT OF PERIPHERAL VASCULAR DISEASE

FR-181877*

230091

2-[6(S)-[3-(Diphenylmethyl)-6-oxo-1,6-dihydropyridazin-1-ylmethyl]-5,6,7,8-tetrahydro-1-naphthoxy]acetic acid



C30 H28 N2 O4; Mol wt: 480.5690

ACTION – Nonprostanoid PGI₂ agonist with K_i values of 94 nM for inhibition of [³H]-iloprost binding to human IP (PGI₂) receptors and of 81 nM for inhibition of ADP-induced aggregation of human platelets. Compound showed excellent pharmacokinetic properties, with good oral bioavailability (56%) and a long half-life (4.3 h) in rats. It showed comparable potency but an improved pharmacokinetic profile and longer half-life than beraprost. Potentially useful as a vasodilator for the treatment of peripheral vascular diseases.

SOURCE – Fujisawa.

REFERENCES

1. Taniguchi, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Naphthalene derivs. as prostaglandin I₂ agonists*. EP 0749424, JP 1997509958, US 5763489, WO 9524393.
2. Tsubaki, K. et al. *A novel pyridazinone derivative as a nonprostanoid PGI₂ agonist*. Bioorg Med Chem Lett 2000, 10(24): 2787.

*Identified compound **230091** (see **228806**) Drug Data Rep 1996, 018(02): 0148.

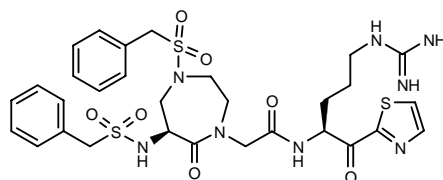
AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

295294

2-[6(S)-(Benzylsulfonamido)-4-(benzylsulfonyl)-7-oxohexahydro-1H-1,4-diazepin-1-yl]-N-[4-(guanidino)-1(S)-(2-thiazolylcarbonyl)butyl]acetamide

2-[N^α-[2-[6(S)-(Benzylsulfonamido)-4-(benzylsulfonyl)-7-oxohexahydro-1H-1,4-diazepin-1-yl]acetyl]-L-arginyl]-thiazole



C30 H38 N8 O7 S3; Mol wt: 718.8772

ACTION – Anticoagulant and antithrombotic agent, a representative compound from a series of cyclic diaza derivatives which are potent inhibitors of factor Xa or factor Xa when assembled in the prothrombinase complex, and which exhibit high selectivity for factor Xa versus other proteases of the coagulation (e.g., thrombin, factor VIIa, factor IXa) or the fibrinolytic cascade (e.g., plasminogen activators, plasmin).

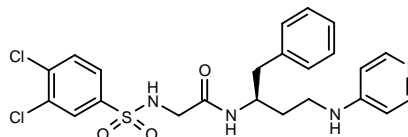
SOURCE – COR Therapeutics.

REFERENCES

1. Scarborough, R.M. and Zhu, B.-Y. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors*. US 6133256.

295299

N-[1(S)-Benzyl-3-(4-pyridinylamino)propyl]-2-(3,4-dichlorophenylsulfonamido)acetamide



C23 H24 Cl2 N4 O3 S; Mol wt: 507.4396

ACTION – Anticoagulant, a representative compound from a series of 4-aminopyridine derivatives with thrombin-inhibitory activity. Potentially useful in the treatment of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation and reocclusion or restenosis of recanalized vessels.

SOURCE – Mediolanum.

REFERENCES

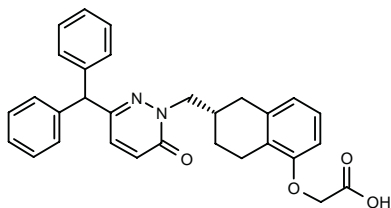
1. Terni, P.M.L. et al. (Mediolanum Farmaceutici) *Selective M2 muscarinic receptor antagonists having 5H-dibenz[b,f]azepine structure*. WO 0102386.
2. Lamperti, G. et al. *Hemodynamic effects of MF 10058, a new cardioselective muscarinic M-2 receptor antagonist, in conscious dogs*. Eur J Pharmacol 2000, 406(1): 93.
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FR-181877*

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1. Taniguchi, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Naphthalene derivs. as prostaglandin I₂ agonists*. EP 0749424, JP 1997509958, US 5763489, WO 9524393.
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*Identified compound **230091** (see **228806**) Drug Data Rep 1996, 018(02): 0148.

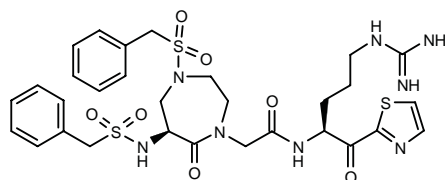
AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

295294

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2-[N^α-[2-[6(S)-(Benzylsulfonamido)-4-(benzylsulfonyl)-7-oxohexahydro-1H-1,4-diazepin-1-yl]acetyl]-L-arginyl]-thiazole



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ACTION – Anticoagulant and antithrombotic agent, a representative compound from a series of cyclic diaza derivatives which are potent inhibitors of factor Xa or factor Xa when assembled in the prothrombinase complex, and which exhibit high selectivity for factor Xa versus other proteases of the coagulation (e.g., thrombin, factor VIIa, factor IXa) or the fibrinolytic cascade (e.g., plasminogen activators, plasmin).

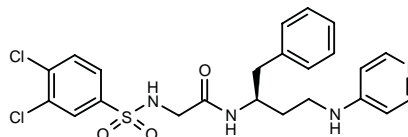
SOURCE – COR Therapeutics.

REFERENCES

1. Scarborough, R.M. and Zhu, B.-Y. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors*. US 6133256.

295299

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C23 H24 Cl2 N4 O3 S; Mol wt: 507.4396

ACTION – Anticoagulant, a representative compound from a series of 4-aminopyridine derivatives with thrombin-inhibitory activity. Potentially useful in the treatment of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation and reocclusion or restenosis of recanalized vessels.

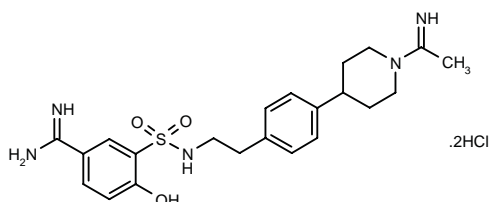
SOURCE – Merck & Co.

REFERENCES

1. Naylor-Olsen, A.M. and Coburn, C. (Merck & Co., Inc.) *Thrombin inhibitors*. US 6133297.

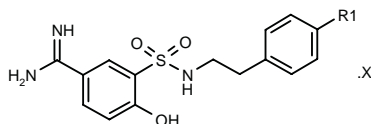
295583

4-Hydroxy-3-[N-[2-[4-[1-(1-iminoethyl)piperidin-4-yl]-phenyl]ethyl]sulfamoyl]benzamidine dihydrochloride



C₂₂ H₂₉ N₅ O₃ S . 2HCl; Mol wt: 516.4909

ACTION – Anticoagulant, a factor Xa inhibitor (IC₅₀ = 87 nM for inhibition of factor Xa vs. IC₅₀ > 100 μM for inhibition of thrombin). Its anticoagulant activity was demonstrated by the ability to prolong the prothrombin time in human plasma. No deaths were observed 24 h after a dose of 30 mg/kg i.v. to rats. Other exemplified compounds from this series of 3-amidinobenzenesulfonamide derivatives are:



Compound	R1	X	Formula
295584	i-Pr	HCl	C ₁₈ H ₂₃ N ₃ O ₃ S.HCl
295585	1-[C(=NH)Me]-3(S)-pyrrolidinyl-O	2HCl	C ₂₁ H ₂₇ N ₅ O ₄ S.2HCl
295586	1-[C(=NH)Me]-4-Pip-O	2HCl	C ₂₂ H ₂₉ N ₅ O ₄ S.2HCl

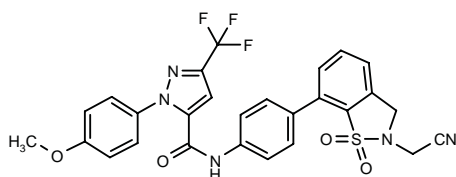
SOURCE – Kissei.

REFERENCES

1. Akahane, S. et al. (Kissei Pharmaceutical Co., Ltd.) *3-Amidinobenzenesulfonamide derivs., medicinal compns. containing the same and intermediates in the production thereof*. WO 0059876.

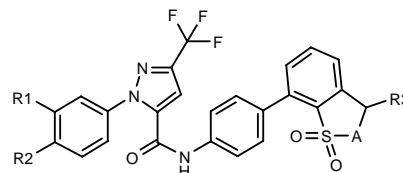
295597

N-[4-[2-(Cyanomethyl)-1,1-dioxo-2,3-dihydro-1,2-benzisothiazol-7-yl]phenyl]-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide

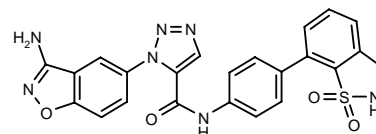


C₂₇ H₂₀ F₃ N₅ O₄ S; Mol wt: 567.5460

ACTION – Anticoagulant, a factor Xa inhibitor that is potentially useful for the treatment of thromboembolic disorders. Other specifically claimed aryl sulfonyl compounds include the following:



Compound	R1	R2	R3	A	Formula
295602	H	OMe	OH	-NH-	C ₂₅ H ₁₉ F ₃ N ₄ O ₅ S
295606	CH ₂ NH ₂	F	H	-NH-	C ₂₅ H ₁₉ F ₄ N ₅ O ₃ S
295608	C(=NH)NH ₂	H	H	-CH ₂ -	C ₂₆ H ₂₀ F ₃ N ₅ O ₃ S
295610	CH ₂ NH ₂	H	H	-N[CH ₂ CH ₂ N(Et) ₂]-	C ₃₁ H ₃₃ F ₃ N ₆ O ₃ S
295613	NH ₂	Cl	H	-CH ₂ -	C ₂₅ H ₁₈ ClF ₃ N ₄ O ₃ S
295614	-C(NH ₂)=NCH=CH-	H	H	-N[CH ₂ CH ₂ N(Et) ₂]-	C ₃₃ H ₃₂ F ₃ N ₇ O ₃ S



295615: C₂₃ H₁₇ N₇ O₄ S

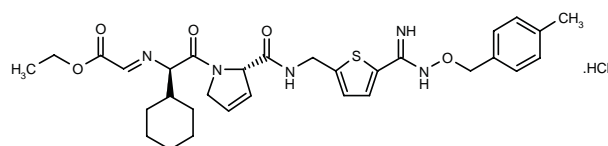
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Wexler, R.R. and Jacobson, I.C. (DuPont Pharmaceuticals Co.) *Aryl sulfonyls as factor Xa inhibitors*. WO 0059902.

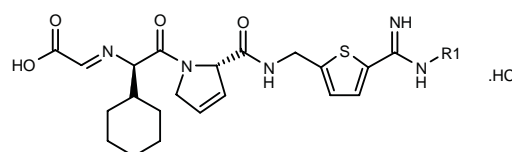
295914

N-(Ethoxycarbonylmethylene)-D-cyclohexylglycyl-L-3,4-didehydroproline 5-[N-(4-methylbenzyloxy)amidino]thien-2-ylmethyl amide hydrochloride

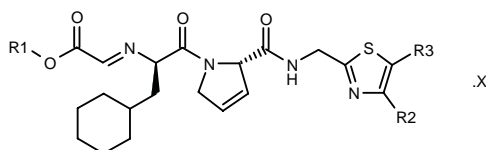


C₃₁ H₃₉ N₅ O₅ S . HCl; Mol wt: 630.2060

ACTION – A representative compound from a series of prodrugs of known 5-membered heterocyclic amidine derivatives with thrombin-inhibitory activity, reported to exhibit improved intestinal absorption and hence increased oral bioavailability relative to the parent compounds. Compound exhibited excellent permeability in a model of *in vitro* intestinal absorption using Caco-2 cells. Other exemplified compounds include the following:



Compound	R1	Formula
295915	i-BuOCO	C ₂₆ H ₃₅ N ₅ O ₅ S.HCl
295916	4-Me-PhCH ₂ O	C ₂₉ H ₃₅ N ₅ O ₅ S.HCl



Compound	R1	R2	R3	X	Formula
295917	C16H33	H	C(=NH)NH2	2HCl	C ₃₇ H ₆₀ N ₆ O ₄ S·2HCl
295918	C16H33	C(=NH)NHOH	H	HCl	C ₃₇ H ₆₀ N ₆ O ₅ S·HCl
295919	C6H13	C(=NH)NHOH	H	HCl	C ₂₇ H ₄₀ N ₆ O ₅ S·HCl
295920	t-BuCH2	C(=NH)NHOH	H	HCl	C ₂₆ H ₃₈ N ₆ O ₅ S·HCl

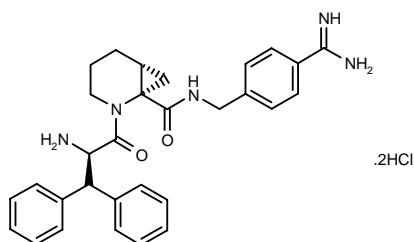
SOURCE – BASF.

REFERENCES

1. Baucke, D. et al. (BASF AG) *Prodrugs of thrombin inhibitors*. WO 0061609.

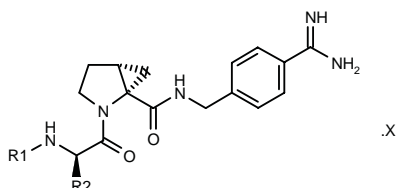
296445

(1*S*,6*R*)-*N*-(4-Amidinobenzyl)-2-[2(*R*)-amino-3,3-diphenylpropionyl]-2-azabicyclo[4.1.0]heptane-1-carboxamide dihydrochloride

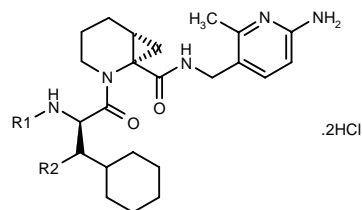


C30 H33 N5 O2 . 2HCl; Mol wt: 568.5455

ACTION – Anticoagulant, a selective thrombin inhibitor (IC₅₀ = 1.0 nM for human thrombin inhibition vs. IC₅₀ > 33,000 nM for plasmin, tPA and vPA inhibition). Its anticoagulant activity was demonstrated *in vitro*, where it doubled human thrombin time at 0.05 μM, and *in vivo*, where it increased thrombin time by 14.2 times at 5 mg/kg p.o. in dogs. Other specifically claimed 2,3-methano-amino acid derivatives are:



Compound	R1	R2	X	Formula
296446	H	CH(Ph)2	2HCl	C ₂₉ H ₃₁ N ₅ O ₂ ·2HCl
296447	CH2CO2H	cyclohexyl	HCl	C ₂₄ H ₃₃ N ₅ O ₄ ·HCl



Compound	R1	R2	Formula
296448	H	H	C ₂₃ H ₃₅ N ₅ O ₂ ·2HCl
296449	Me	H	C ₂₄ H ₃₇ N ₅ O ₂ ·2HCl
296450	H	cyclohexyl	C ₂₉ H ₄₅ N ₅ O ₂ ·2HCl

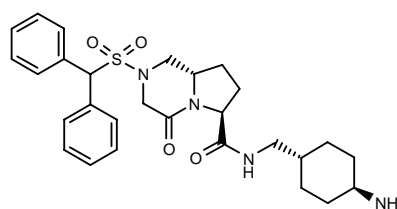
SOURCE – ADIR.

REFERENCES

1. De Nanteuil, G. et al. (ADIR et Cie.) *2,3-Methano-amino acid derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 1050534, FR 2793248, JP 2000344745.

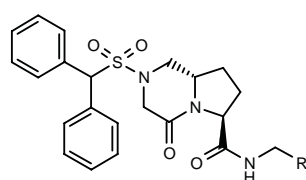
297831

(6*S*,8*aS*)-*N*-(*trans*-4-Aminocyclohexylmethyl)-2-(diphenylmethylsulfonyl)-4-oxooctahydropyrrolo[1,2-*a*]-pyrazine-6-carboxamide



C28 H36 N4 O4 S; Mol wt: 524.6824

ACTION – Potent and selective, nonpeptide inhibitor of human thrombin (K_i = 9.18 nM) with little or no activity against other serine proteases (K_i > 4 μM against trypsin, factor Xa, and activated protein C). It inhibited both free and clot-bound human thrombin with IC₅₀ values of 508 and 212 nM, respectively. Compound specifically inhibited thrombin-induced aggregation of rat (IC₅₀ = 20.6 nM) and human platelets (IC₅₀ = 70.6 nM), but had no effect against ADP-induced human platelet aggregation. Concentration-dependent prolongation of rat and human plasma clotting times was seen. *In vivo* in rat models of arterial and venous thrombosis, compound proved to be an effective antithrombotic agent following i.v. administration, but it had low oral bioavailability (2%). Other representative bicyclic lactam inhibitors are:



Compound	R1	Formula
297829	1-[HONHC(=NH)]-4-Pip	C ₂₈ H ₃₆ N ₆ O ₅ S
297830	4-[NH2C(=NH)]-Ph	C ₂₉ H ₃₁ N ₅ O ₄ S

SOURCE – BioChem Pharma.

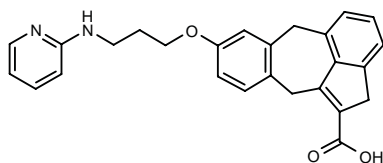
REFERENCES

1. Leblond, L. et al. *In vitro and in vivo properties of bicyclic lactam inhibitors: A novel class of low molecular weight peptidomimetic thrombin inhibitors*. *Thromb Res* 2000, 100(3): 195.

ANTIPLATELET THERAPY

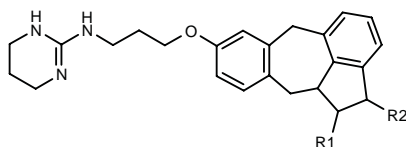
296254

8-[3-(2-Pyridinylamino)propoxy]-6,11-dihydro-2*H*-dibenzo-[*cd,g*]azulene-1-carboxylic acid



C26 H24 N2 O3; Mol wt: 412.4866

ACTION – An inhibitor of integrins, particularly gpIIb/IIIa, $\alpha_v\beta_3$ and $\alpha_v\beta_5$, with potential for the treatment of cardiovascular disorders, thrombosis, myocardial infarction, coronary heart diseases, arteriosclerosis, osteoporosis and cancer. Other specifically claimed compounds from this series of dibenzoazulene derivatives are:



Compound	R1	R2	Formula
296256	CO2H	H	C ₂₅ H ₂₉ N ₃ O ₃
296257	H	CH2CO2H	C ₂₆ H ₃₁ N ₃ O ₃

SOURCE – Merck KGaA.

REFERENCES

1. Stähle, W. et al. (Merck Patent GmbH) *Dibenzoazulene derivs. for treating thrombosis, osteoporosis, arteriosclerosis*. DE 19916837, WO 0063178.

RENAL–UROLOGIC DRUGS

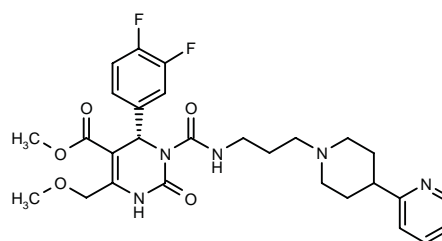
BENIGN PROSTATIC HYPERPLASIA THERAPY

L-771688

288343

4(*S*)-(3,4-Difluorophenyl)-6-(methoxymethyl)-2-oxo-3-[3-[4-(2-pyridinyl)piperidin-1-yl]propylcarbamoyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

SNAP-6383



C28 H33 F2 N5 O5; Mol wt: 557.5947

ACTION – Potent and highly selective α_{1A} -adrenoceptor antagonist, as shown in binding studies using human, rat and dog α_{1A} -adrenoceptors (K_i = 1 nM or less) and α_{1B} - and α_{1D} -adrenoceptors (K_i = 360-1000 nM). Compound competitively antagonized norepinephrine-induced inositol phosphate formation in CHO cells expressing human α_{1A} -adrenoceptors (K_b = 0.02 nM), while having much weaker activity in cells expressing the other α_1 -adrenoceptor subtypes (K_b = 84-3200 nM). It also antagonized phenylephrine- and A-61603-induced contractions in dog, rat and human isolated prostate, human and monkey bladder neck and rat caudal artery (K_b = 0.02-0.3 nM), but not norepinephrine-induced contractions in isolated rat aorta; competitive antagonism was observed in most tissues. In a short-term clinical trial in patients with benign prostatic hyperplasia (BPH), single oral doses of compound (5, 20 mg) were well tolerated and dose-dependently increased peak urine flow rate at 4-6 h postdose.

SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Broten, T.P. et al. (Merck & Co., Inc.) *Combination therapy for the treatment of benign prostatic hyperplasia*. WO 9948530.
2. Cui, D. et al. (Synaptic Pharmaceutical Corp.; Merck & Co., Inc.) *Dihydropyrimidines and uses thereof*. WO 0037026.
3. Sidler, D.R. et al. (Merck & Co., Inc.) *α_{1A} Adrenergic receptor antagonist*. WO 9907695.
4. Wong, W.C. et al. (Synaptic Pharmaceutical Corp.) *Dihydropyrimidines and uses thereof*. EP 1021185, JP 2000506904, WO 9742956.
5. Wong, W.C. et al. (Synaptic Pharmaceutical Corp.) *Dihydropyrimidines and uses thereof*. WO 9851311.
6. Chang, R.S.L. et al. *In vitro studies on L-771,688 (SNAP 6383), a new potent and selective α_{1A} -adrenoceptor antagonist*. *Eur J Pharmacol* 2000, 409(3): 301.

SOURCE – BioChem Pharma.

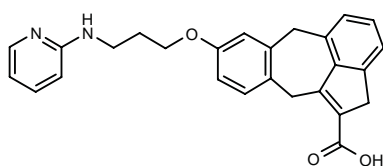
REFERENCES

1. Leblond, L. et al. *In vitro and in vivo properties of bicyclic lactam inhibitors: A novel class of low molecular weight peptidomimetic thrombin inhibitors*. *Thromb Res* 2000, 100(3): 195.

ANTIPLATELET THERAPY

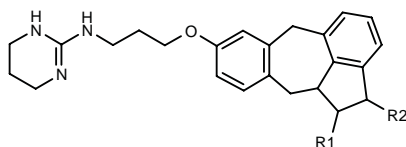
296254

8-[3-(2-Pyridinylamino)propoxy]-6,11-dihydro-2*H*-dibenzo-[*cd*,*g*]azulene-1-carboxylic acid



C26 H24 N2 O3; Mol wt: 412.4866

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SOURCE – Merck KGaA.

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RENAL–UROLOGIC DRUGS

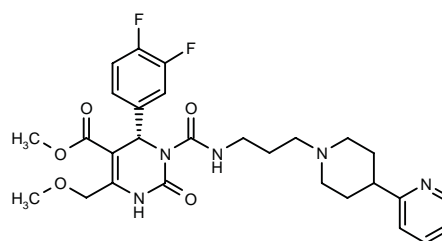
BENIGN PROSTATIC HYPERPLASIA THERAPY

L-771688

288343

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SNAP-6383



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5. Wong, W.C. et al. (Synaptic Pharmaceutical Corp.) *Dihydropyrimidines and uses thereof*. WO 9851311.
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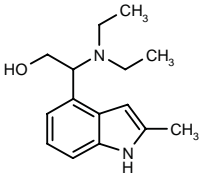
7. Marks, L.S. et al. *Effects of a highly selective α_{1A} antagonist on urinary flow rate in men with symptomatic BPH.* J Urol 2000, 163(4, Suppl.): Abst 1369.

8. Wagner, J.A. et al. *Increased L-771688 plasma concentrations with ketoconazole coadministration.* Clin Pharmacol Ther 2001, 69(2): Abst PIII-26.

TREATMENT OF URINARY INCONTINENCE

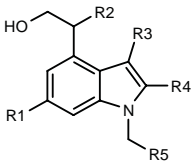
295900

2-(Diethylamino)-2-(2-methyl-1*H*-indol-4-yl)ethan-1-ol



C15 H22 N2 O; Mol wt: 246.3518

ACTION – Agent with strong urethral contractile activity and weak arterial contractile activity, with additional vasoconstrictive activity, as demonstrated in a panel of *in vitro* and *in vivo* assays. Potentially useful for the treatment of urinary incontinence, with reduced cardiovascular side effects compared to conventional agents, as well as for the treatment of venous insufficiency, migraine, gastrointestinal disorders and as a nasal vasoconstrictor. Other specifically claimed compounds from this series of 1-aminoethylindole derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
295901	H	N(Et)2	H	Et	H	C ₁₇ H ₂₆ N ₂ O
295902	H	N(Et)2	H	Ph	H	C ₂₁ H ₂₆ N ₂ O
295903	H	N(Et)2	H	Me	H	C ₁₆ H ₂₄ N ₂ O
295904	H	N(Et)2	H	Me	Me	C ₁₇ H ₂₆ N ₂ O
295905	H	N(Et)2	F	Me	H	C ₁₆ H ₂₃ FN ₂ O
295906	H	2(R)-Me-1-Pip	H	Me	H	C ₁₈ H ₂₆ N ₂ O
295907	OH	N(Et)2	H	Me	H	C ₁₆ H ₂₄ N ₂ O ₂

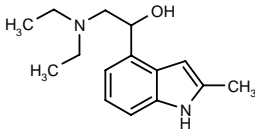
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Bovy, P.R. et al. (Sanofi-Synthélabo) *1-Amino ethylindole derivs. for the treatment of urinary incontinence.* FR 2792316, WO 0061554.

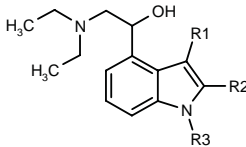
295908

2-(Diethylamino)-1-(2-methyl-1*H*-indol-4-yl)ethan-1-ol



C15 H22 N2 O; Mol wt: 246.3518

ACTION – Agent with strong urethral contractile activity and weak arterial contractile activity, with additional vasoconstrictive activity, as demonstrated in a panel of *in vitro* and *in vivo* assays. Potentially useful for the treatment of urinary incontinence, with reduced cardiovascular side effects compared to conventional agents, as well as for the treatment of venous insufficiency, migraine, gastrointestinal disorders and as a nasal vasoconstrictor. Other specifically claimed compounds from this series of 2-aminoethylindole derivatives are:



Compound	R1	R2	R3	Formula
295909	H	Et	Me	C ₁₇ H ₂₆ N ₂ O
295910	H	Ph	Me	C ₂₁ H ₂₆ N ₂ O
295911	H	Me	Me	C ₁₆ H ₂₄ N ₂ O
295912	H	Me	Et	C ₁₇ H ₂₆ N ₂ O
295913	F	Me	Me	C ₁₆ H ₂₃ FN ₂ O

SOURCE – Sanofi-Synthélabo.

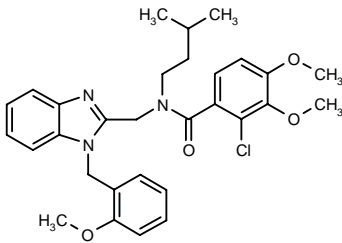
REFERENCES

1. Mougenot, P. et al. (Sanofi-Synthélabo) *2-Aminoethyl-indole derivs., their preparation and therapeutic use.* FR 2792313, WO 0061553.

TREATMENT OF RENAL DISEASES

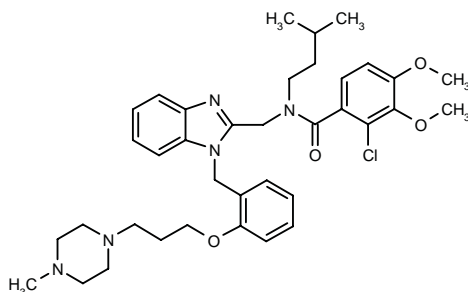
295595

2-Chloro-*N*-isopentyl-3,4-dimethoxy-*N*-[1-(2-methoxybenzyl)-1*H*-benzimidazol-2-ylmethyl]benzamide



C30 H34 Cl N3 O4; Mol wt: 536.0686

ACTION – Selective modulator of bradykinin B₂ receptors, potentially useful for the treatment or diagnosis of renal diseases, heart failure, hypertension, Meniere's disease, vaginal inflammation and pain, peripheral circulatory disorders, climacteric disorders, myocardial infarction, angina pectoris, restenosis following PTCA, hepatitis, liver cirrhosis, pancreatitis, diabetes and complications thereof, male infertility, glaucoma, etc., for increasing blood–brain barrier permeability and in the treatment of pain, asthma and rhinitis. The invention also provides tools for the localization of B₂ receptors. Another compound from this series of aryl and heteroaryl fused aminoalkyl-imidazole derivatives is:



295596: C₃₇ H₄₈ Cl N₅ O₄

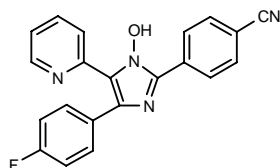
SOURCE – Neurogen.

REFERENCES

1. Hutchison, A. et al. (Neurogen Corp.) Aryl and heteroaryl fused aminoalkyl-imidazole derivs: Selective modulators of bradykinin B₂ receptors. WO 0059886.

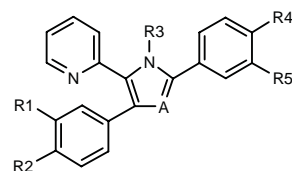
295893

4-[4-(4-Fluorophenyl)-1-hydroxy-5-(2-pyridinyl)-1H-imidazol-2-yl]benzonitrile



C₂₁ H₁₃ F N₄ O; Mol wt: 356.3587

ACTION – An inhibitor of the transforming growth factor-β (TGF-β) signaling pathway via inhibition of the phosphorylation of smad2 or smad3 by the type 1 or activin-like kinase ALK5 receptor, with potential in the treatment or prevention of a broad range of disorders mediated by ALK5 kinase mechanisms such as chronic and acute renal diseases, wound healing, arthritis, osteoporosis, congestive heart failure, ulcers, ocular disorders, diabetic nephropathy, Alzheimer's disease, atherosclerosis, fibrosis and restenosis, as well as for inhibiting matrix formation. Other specifically claimed compounds from this series of 2-pyridyl-substituted triarylimidazoles include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
295894	H	F	H	CO ₂ Et	H	N	C ₂₃ H ₁₈ FN ₃ O ₂
295895	-OCH ₂ O-		H	H	NH ₂	N	C ₂₁ H ₁₆ N ₄ O ₂
295896	-OCH ₂ CH ₂ O-		H	CN	H	N	C ₂₃ H ₁₆ N ₄ O ₂
295897	-OCH ₂ CH ₂ -		H	CONH ₂	H	N	C ₂₃ H ₁₈ N ₄ O ₂
295898	-OCH ₂ CH ₂ O-		Me	CONH ₂	H	N	C ₂₄ H ₂₀ N ₄ O ₃
295899	-OCH ₂ O-		H	CONH ₂	H	CH	C ₂₃ H ₁₇ N ₃ O ₃

SOURCE – GlaxoSmithKline.

REFERENCES

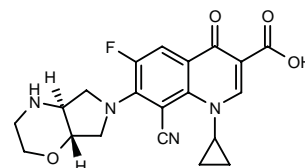
1. Burgess, J.L. and Callahan, J.F. (SmithKline Beecham Corp.) Triarylimidazoles. WO 0061576.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

295632

(4a*S*,7a*S*)-8-Cyano-1-cyclopropyl-6-fluoro-4-oxo-7-(perhydropyrrolo[3,4-*b*]-1,4-oxazin-6-yl)-1,4-dihydroquinoline-3-carboxylic acid



C₂₀ H₁₉ F N₄ O₄; Mol wt: 398.3921

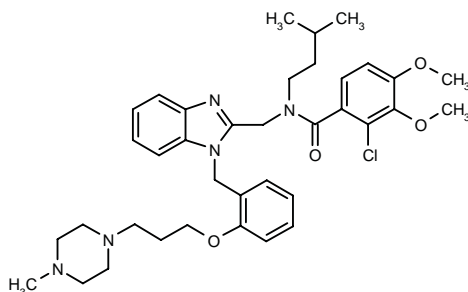
ACTION – An exemplified compound from a series of quinolone- and naphthyridone-carboxylic acids with a 2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl moiety at the 7-position and high activity against *Helicobacter pylori*. Compound gave an MIC value of 0.06 mg/ml against an *H. pylori* clinical isolate and exhibited high activity in mice infected with *Helicobacter felis* ATCC 49179, a 10-day treatment with 10 mg/kg b.i.d. providing bacterial eradication.

SOURCE – Bayer.

REFERENCES

1. Matzke, M. et al. (Bayer AG) Use of 7-(2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-quinolone carboxylic acid and naphthyridone carboxylic acid derivs. for the treatment of *Helicobacter pylori* infections and associated gastroduodenal diseases. DE 19652239, JP 2000351781, JP 2000514825, US 6133260, WO 9826779.

ACTION – Selective modulator of bradykinin B₂ receptors, potentially useful for the treatment or diagnosis of renal diseases, heart failure, hypertension, Meniere's disease, vaginal inflammation and pain, peripheral circulatory disorders, climacteric disorders, myocardial infarction, angina pectoris, restenosis following PTCA, hepatitis, liver cirrhosis, pancreatitis, diabetes and complications thereof, male infertility, glaucoma, etc., for increasing blood–brain barrier permeability and in the treatment of pain, asthma and rhinitis. The invention also provides tools for the localization of B₂ receptors. Another compound from this series of aryl and heteroaryl fused aminoalkyl-imidazole derivatives is:



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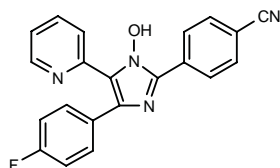
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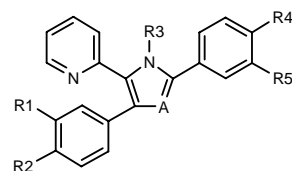
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295896	-OCH ₂ CH ₂ O-		H	CN	H	N	C ₂₃ H ₁₆ N ₄ O ₂
295897	-OCH ₂ CH ₂ -		H	CONH ₂	H	N	C ₂₃ H ₁₈ N ₄ O ₂
295898	-OCH ₂ CH ₂ O-		Me	CONH ₂	H	N	C ₂₄ H ₂₀ N ₄ O ₃
295899	-OCH ₂ O-		H	CONH ₂	H	CH	C ₂₃ H ₁₇ N ₃ O ₃

SOURCE – GlaxoSmithKline.

REFERENCES

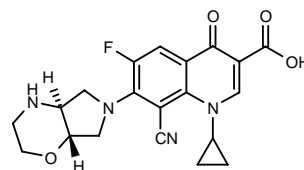
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

295632

(4a*S*,7a*S*)-8-Cyano-1-cyclopropyl-6-fluoro-4-oxo-7-(perhydropyrrolo[3,4-*b*]-1,4-oxazin-6-yl)-1,4-dihydroquinoline-3-carboxylic acid



C₂₀ H₁₉ F N₄ O₄; Mol wt: 398.3921

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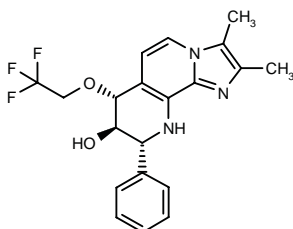
SOURCE – Bayer.

REFERENCES

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296365

2,3-Dimethyl-9(*R*)-phenyl-7(*R*)-(2,2,2-trifluoroethoxy)-7,8,9,10-tetrahydroimidazo[1,2-*h*][1,7]naphthyridin-8(*R*)-ol



C20 H20 F3 N3 O2; Mol wt: 391.3910

ACTION – Gastric antisecretory agent proven to induce 100% inhibition of pentagastrin-stimulated gastric acid secretion in perfused rat stomach *in vivo* at 3 µmol/kg i.v. Potentially useful for the treatment of gastrointestinal inflammatory diseases and lesions, e.g., gastric and duodenal ulcer, gastritis and functional gastropathy due to hyperacidity or medicaments. A representative compound from a series of haloalkoxyimidazonaphthyridines.

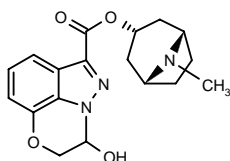
SOURCE – Byk Gulden.

REFERENCES

1. Grundler, G. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Haloalkoxyimidazonaphthyridines*. WO 0063211.

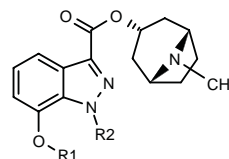
AGENTS FOR IRRITABLE BOWEL SYNDROME**296193**

3-Hydroxy-2,3-dihydropyrazolo[1,5,4-*de*]-1,4-benzoxazine-6-carboxylic acid *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester



C18 H21 N3 O4; Mol wt: 343.3809

ACTION – Agent for the treatment of functional disorders of the gastrointestinal tract such as intestinal motor and secretory disorders, irritable bowel syndrome, intestinal pain, diarrhea and reflux esophagus, among others, a combined 5-HT₃ and 5-HT₄ receptor antagonist. Other specifically claimed compounds from this series of indazole derivatives are:



Compound	R1	R2	Formula
296195	H	CH ₂ CH ₂ OH	C ₁₈ H ₂₃ N ₃ O ₄
296196	H	CH ₂ CO ₂ H	C ₁₈ H ₂₁ N ₃ O ₅
296197	CH ₂ CH ₂ OH	H	C ₁₈ H ₂₃ N ₃ O ₄
296198	CH ₂ CO ₂ H	H	C ₁₈ H ₂₁ N ₃ O ₅

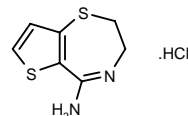
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Zard, L. (Sanofi-Synthélabo) *Indazole derivs., preparation and therapeutic application thereof*. FR 2792318, WO 0063215.

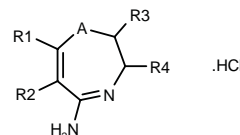
AGENTS FOR INFLAMMATORY BOWEL DISEASE**296503**

2,3-Dihydrothieno[2,3-*f*][1,4]thiazepin-5-ylamine hydrochloride



C7 H8 N2 S2 . HCl; Mol wt: 220.7471

ACTION – Nitric oxide synthase (NOS) inhibitor that inhibits the inducible isoform (iNOS), potentially useful for the treatment or prevention of inflammatory diseases, preferably inflammatory bowel disease, rheumatoid arthritis and osteoarthritis, as well as for the therapy of pain. Other exemplified 5,7-bicyclic amidine derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
296504	-CH=CHS-		H	Pr	S	C ₁₀ H ₁₄ N ₂ S ₂ .HCl
296505	-CH=CHS-		Me	H	O	C ₈ H ₁₀ N ₂ OS.HCl
296507	-N(Me)-CH=CH-		H	allyl	CH ₂	C ₁₂ H ₁₇ N ₃ .HCl
296508	-CH=CHS-		H	Pr	CH ₂	C ₁₁ H ₁₆ N ₂ S.HCl
296509	-CH=CHS-		H	4-CN-PhOCH ₂	O	C ₁₅ H ₁₃ N ₃ O ₂ S.HCl
296510	-CH=CHS-		6-MeO-3-Pyr-CH=CHCH ₂ CH ₂	H	O	C ₁₇ H ₁₉ N ₃ O ₂ S.HCl
296511	-CH=CHS-		CH ₂ NHCONH ₂	H	O	C ₉ H ₁₂ N ₄ O ₂ S.HCl
296512	-CH=CHS-		(CH ₂) ₂ NHCOPh	H	O	C ₁₆ H ₁₇ N ₃ O ₂ S.HCl

SOURCE – AstraZeneca.

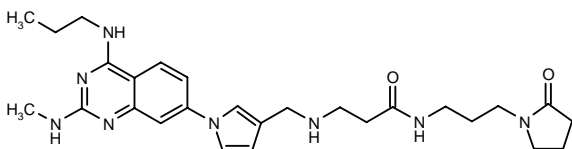
REFERENCES

1. Cheshire, D. et al. (AstraZeneca AB; AstraZeneca plc) 5,7-Bicyclic amidine derivs. useful as nitric oxide synthase inhibitors. WO 0064904.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

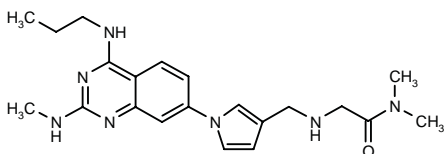
296985

N^3 -[1-[2-(Methylamino)-4-(propylamino)quinazolin-7-yl]-1H-pyrrol-3-ylmethyl]- N^1 -[3-(2-oxopyrrolidin-1-yl)propyl]- β -alaninamide



C27 H38 N8 O2; Mol wt: 506.6512

ACTION – Potent and selective 5-HT₄ agonist with nanomolar binding affinity (K_i = 35 nM for guinea pig striatal 5-HT₄ receptors) and functional activity (EC_{30} = 37 nM for relaxation of rat esophageal tunica muscularis mucosae). *In vivo*, compound was seen to enhance gastrointestinal motor activity in conscious dogs. Potentially useful as a gastrointestinal prokinetic agent. Another related quinazoline derivative is:



296986: C21 H29 N7 O

SOURCE – Kyowa Hakko.

REFERENCES

1. Koshimura, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) Quinazoline derivs. WO 9950264.
2. Koshimura, H. et al. *Synthetic studies of quinazoline derivatives as 5-HT₄ agonist*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 2P-23.

VISICOL™

272926

Sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP

INKP-100

Diacol (former brand name)

ACTION – Colonic purgative.

INDICATIONS – Cleansing of the colon prior to colonoscopy in adults 18 years and older.

PRESENTATION – Tablets containing 1.102 g sodium phosphate monobasic monohydrate and 0.398 g sodium phosphate dibasic anhydrous, for a total of 1.5 g sodium phosphate.

PROPRIETARY NAME – Visicol (US).

SOURCES – InKine; copromoted by Procter & Gamble.

REFERENCES

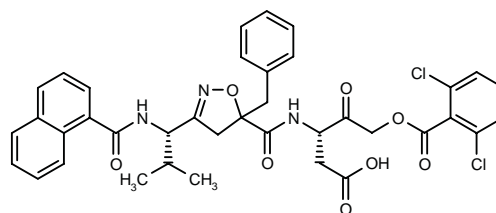
1. Kastenber, D. et al. *Sodium phosphate tablets (INKP-100, Diacol™) are safe and effective as a purgative for colonoscopy*. 64th Annu Sci Meet Am Coll Gastroenterol (Oct 18-20, Phoenix) 1999, Abst P495.
2. *Enrollment completed for trial of InKine purgative tablets*. DailyDrugNews.com (Daily Essentials) 1999, March 29.
3. *FDA accepts InKine's Diacol NDA for filing*. DailyDrugNews.com (Daily Essentials) 2000, Jan 26.
4. *FDA approves Visicol*. DailyDrugNews.com (Daily Essentials) 2000, Sept 29.
5. *First tablet preparation for bowel cleansing prior to colonoscopy now available in U.S.*. DailyDrugNews.com (Daily Essentials) 2001, Jan 17.
6. *InKine colonic purgative proceeds to phase III trials*. DailyDrugNews.com (Daily Essentials) 1998, Oct 8.
7. *InKine completes enrollment of first pivotal phase III clinical trial of Diacol*. DailyDrugNews.com (Daily Essentials) 1999, March 18.
8. *InKine changes trade name of Diacol to Visicol*. DailyDrugNews.com (Daily Essentials) 2000, Aug 29.
9. *InKine schedules pre-NDA meeting with FDA for INKP-100*. DailyDrugNews.com (Daily Essentials) 1999, Feb 26.
10. *InKine seeks FDA approval of Diacol*. DailyDrugNews.com (Daily Essentials) 1999, Nov 24.
11. *InKine: Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1998, Nov 2.
12. *New clinical study evaluating INKP-100 now in progress*. DailyDrugNews.com (Daily Essentials) 1998, Aug 21.
13. *Phase IIb trial results confirm efficacy and safety of INKP-100 for colonoscopy*. DailyDrugNews.com (Daily Essentials) 1998, Sept 21.
14. *Pivotal results demonstrate equal efficacy and better tolerability of Diacol versus NuLYTELY*. DailyDrugNews.com (Daily Essentials) 1999, May 3.
15. *Product development and research programs*. InKine Product Pipeline 2000, Nov 10.
16. *Visicol to be copromoted by Procter & Gamble*. DailyDrugNews.com (Daily Essentials) 2001, Feb 19.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

XYZ-033MP

298268

3(S)-[5-Benzyl-3-[2-methyl-1(S)-(1-naphthylcarboxamido)propyl]-4,5-dihydroisoxazol-5-ylcarboxamido]-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid



C38 H35 Cl2 N3 O8; Mol wt: 732.6135

ACTION – Broad-spectrum nonpeptide caspase inhibitor that is able to protect rat hepatocytes from apoptotic death induced by TNF- α plus actinomycin D. *In vivo* studies in mice with concanavalin A-induced hepatitis showed not only protection, but also hepatocyte rescue from lethal apoptosis, without toxic effects to the liver; it suppressed the ConA-induced elevation in serum IL-1 β levels. Potentially useful for the treatment of fulminant hepatic failure.

SOURCE – LG Chem.

REFERENCES

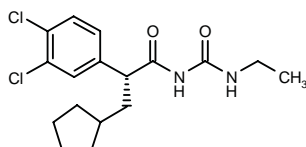
- Kim, E.E.-K. et al. (LG Chem Ltd.) *Caspase inhibitor*. WO 0121599, WO 0121600.
- Kim, K.M. et al. A broad-spectrum caspase inhibitor blocks concanavalin A-induced hepatitis in mice. *Clin Immunol* 2000, 97(3): 221.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

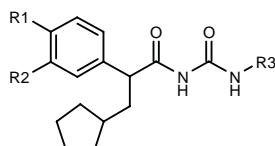
295397

N-[3-Cyclopentyl-2(*R*)-(3,4-dichlorophenyl)propionyl]-*N'*-ethylurea



C17 H22 Cl2 N2 O2; Mol wt: 357.2788

ACTION – Agent for the treatment of type 2 diabetes that acts by increasing insulin secretion via glucokinase (GK) activation. *In vitro*, compound was shown to produce a 50% increase in human liver GK1 activity at a concentration of 30 μ M or less, and *in vivo* it exhibited excellent GK-activating activity in mice at 50 mg/kg p.o., as measured by a significant decrease in blood glucose levels. Other specifically claimed compounds from this broad series of amide and urea derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
295398	Cl	Cl	Me	R	C ₁₆ H ₂₀ Cl ₂ N ₂ O ₂
295399	Cl	Cl	Me		C ₁₆ H ₂₀ Cl ₂ N ₂ O ₂
295400	SO ₂ Me	H	Me		C ₁₇ H ₂₄ N ₂ O ₄ S
295401	Cl	Cl	allyl	R	C ₁₈ H ₂₂ Cl ₂ N ₂ O ₂
295402	SO ₂ Me	Cl	Me		C ₁₇ H ₂₃ ClN ₂ O ₄ S
295403	SO ₂ Me	Cl	Me	R	C ₁₇ H ₂₃ ClN ₂ O ₄ S
295404	SO ₂ Me	Br	Me		C ₁₇ H ₂₃ BrN ₂ O ₄ S

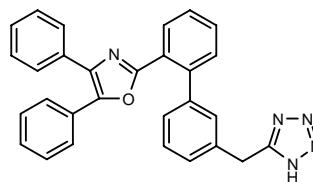
SOURCE – Roche.

REFERENCES

- Bizzarro, F.T. et al. (F. Hoffmann-La Roche AG) *Glucokinase activators*. WO 0058293.

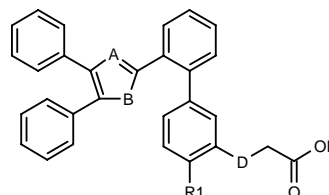
295458

5-[2'-(4,5-Diphenyloxazol-2-yl)biphenyl-3-ylmethyl]-1*H*-tetrazole

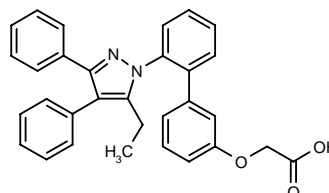


C29 H21 N5 O; Mol wt: 455.5189

ACTION – An inhibitor of aP2 (adipocyte fatty binding protein), an abundant cytosolic protein in adipocytes that is involved in the regulation of fatty acid trafficking in adipocytes and mediates fatty acid fluxes in adipose tissue, with potential for the treatment of diabetes, particularly type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, obesity, syndrome X, diabetic complications, atherosclerosis and related diseases, and other chronic inflammatory and autoimmune diseases. Other specifically claimed compounds from this series of heterocyclic-containing biphenyl derivatives include the following:



Compound	R1	A	B	D	Formula
295459	H	N	N(Et)	O	C ₃₁ H ₂₆ N ₂ O ₃
295460	H	N	O	CH ₂	C ₃₀ H ₂₃ NO ₃
295461	Me	N	O	NH	C ₃₀ H ₂₄ N ₂ O ₃
295462	H	N	NH	NH	C ₂₉ H ₂₃ N ₃ O ₂
295463	H	N	N(i-Bu)	NH	C ₃₃ H ₃₁ N ₃ O ₂
295464	H	N	N(CH ₂ OMe)	O	C ₃₁ H ₂₆ N ₂ O ₄
295465	H	C(Et)	NH	O	C ₃₂ H ₂₇ NO ₃
295466	H	N	N(CH ₂ CH ₂ F)	CH ₂	C ₃₂ H ₂₇ FN ₂ O ₂



295467: C₃₁ H₂₆ N₂ O₃

SOURCE – Bristol-Myers Squibb.

REFERENCES

- Robl, J.A. et al. (Bristol-Myers Squibb Co.) *Heterocyclic containing biphenyl aP2 inhibitors and method*. WO 0059506.

ACTION – Broad-spectrum nonpeptide caspase inhibitor that is able to protect rat hepatocytes from apoptotic death induced by TNF- α plus actinomycin D. *In vivo* studies in mice with concanavalin A-induced hepatitis showed not only protection, but also hepatocyte rescue from lethal apoptosis, without toxic effects to the liver; it suppressed the ConA-induced elevation in serum IL-1 β levels. Potentially useful for the treatment of fulminant hepatic failure.

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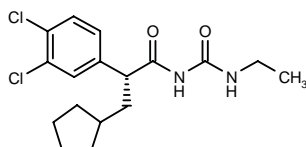
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

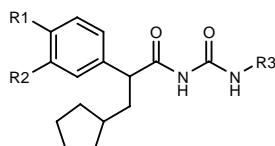
295397

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295401	Cl	Cl	allyl	R	C ₁₈ H ₂₂ Cl ₂ N ₂ O ₂
295402	SO ₂ Me	Cl	Me		C ₁₇ H ₂₃ ClN ₂ O ₄ S
295403	SO ₂ Me	Cl	Me	R	C ₁₇ H ₂₃ ClN ₂ O ₄ S
295404	SO ₂ Me	Br	Me		C ₁₇ H ₂₃ BrN ₂ O ₄ S

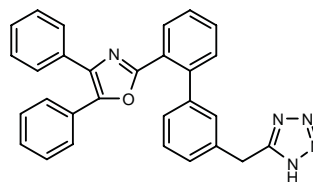
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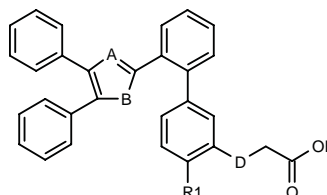
295458

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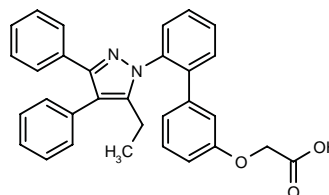


C29 H21 N5 O; Mol wt: 455.5189

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Compound	R1	A	B	D	Formula
295459	H	N	N(Et)	O	C ₃₁ H ₂₆ N ₂ O ₃
295460	H	N	O	CH ₂	C ₃₀ H ₂₃ NO ₃
295461	Me	N	O	NH	C ₃₀ H ₂₄ N ₂ O ₃
295462	H	N	NH	NH	C ₂₉ H ₂₃ N ₃ O ₂
295463	H	N	N(i-Bu)	NH	C ₃₃ H ₃₁ N ₃ O ₂
295464	H	N	N(CH ₂ OMe)	O	C ₃₁ H ₂₆ N ₂ O ₄
295465	H	C(Et)	NH	O	C ₃₂ H ₂₇ NO ₃
295466	H	N	N(CH ₂ CH ₂ F)	CH ₂	C ₃₂ H ₂₇ FN ₂ O ₂



295467: C₃₁ H₂₆ N₂ O₃

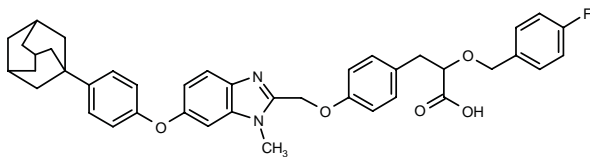
SOURCE – Bristol-Myers Squibb.

REFERENCES

- Robl, J.A. et al. (Bristol-Myers Squibb Co.) *Heterocyclic containing biphenyl aP2 inhibitors and method*. WO 0059506.

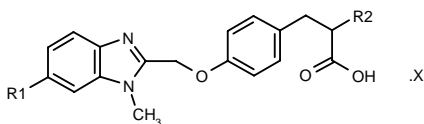
295588

3-[4-[6-[4-(1-Adamantyl)phenoxy]-1-methyl-1*H*-benzimidazol-2-yl)methoxy]phenyl]-2-(4-fluorobenzyloxy)-propionic acid



C41 H41 F N2 O5; Mol wt: 660.7819

ACTION – Agent for the treatment of diabetes and impaired glucose tolerance found to lower blood glucose levels by 58.5% at a concentration of 0.01% in the diet for 3 days in diabetic mice. Other exemplified α -substituted carboxylic acid derivatives are:



Compound	R1	R2	X	Formula
295590	3,5-(<i>t</i> -Bu)2-4-OH-PhS	4-F-PhCH2O		C ₃₉ H ₄₃ FN ₂ O ₅ S
295591	OMe	OEt	HCl	C ₂₁ H ₂₄ N ₂ O ₅ ·HCl
295593	OMe	2-(PhCO)-PhNH	HCl	C ₃₂ H ₂₉ N ₃ O ₅ ·HCl
295594	3,5-(Me)2-4-NH2-PhO	2-(PhCO)-PhNH	2HCl	C ₃₉ H ₃₆ N ₄ O ₅ ·2HCl

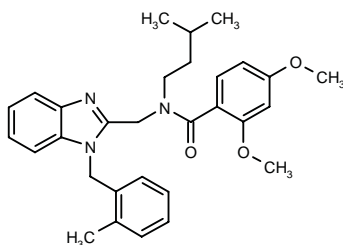
SOURCE – Sankyo.

REFERENCES

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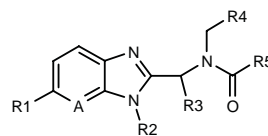
295598

N-Isopentyl-2,4-dimethoxy-*N*-[1-(2-methylbenzyl)-1*H*-benzimidazol-2-ylmethyl]benzamide



C30 H35 N3 O3; Mol wt: 485.6245

ACTION – Antidiabetic agent, a modulator of blood glucose levels that binds to G-protein-coupled receptors, preferably GLP-1 receptors. Potentially useful for the treatment of type 2 diabetes, obesity and eating disorders, as well as for the localization of cellular receptors that are involved in the modulation of blood glucose levels. Other exemplified aryl and heteroaryl fused aminoalkyl-imidazole derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
295599	H	Pr	Me	H	2,3-(Me)2-Ph-OCH2	CH	C ₂₃ H ₂₉ N ₃ O ₂
295600	H	cyclopropyl-CH2	Me	H	2,3-(Me)2-Ph-OCH2	CH	C ₂₄ H ₂₉ N ₃ O ₂
295601	H	2-Cl-PhCH2	H	<i>i</i> -Bu	2,4-(MeO)2-Ph	CH	C ₂₉ H ₃₂ ClN ₃ O ₃
295603	H	2-Me-PhCH2	H	<i>i</i> -Bu	2,4-(MeO)2-Ph	N	C ₂₉ H ₃₄ N ₄ O ₃
295604	H	Pr	Me	H	2,3-(Me)2-Ph-OCH2	N	C ₂₂ H ₂₈ N ₄ O ₂
295605	Cl	cyclopentyl	Me	H	2,3-(Me)2-Ph-OCH2	CH	C ₂₅ H ₃₀ ClN ₃ O ₂

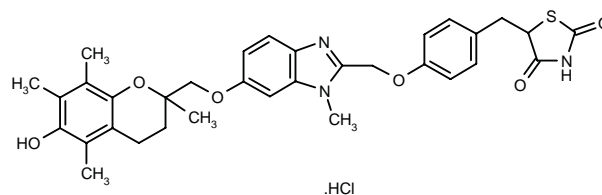
SOURCE – Neurogen.

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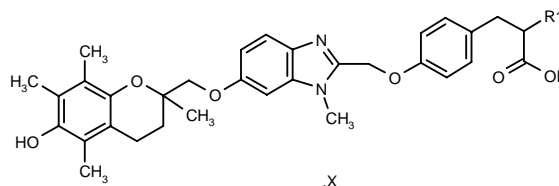
295968

5-[4-[6-(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethoxy)-1-methyl-1*H*-benzimidazol-2-ylmethoxy]benzyl]thiazolidine-2,4-dione hydrochloride



C33 H35 N3 O6 S · HCl; Mol wt: 638.1814

ACTION – Blood glucose-lowering agent, potentially useful for the treatment of diabetes, obesity, impaired glucose tolerance and related disorders. The compound lowered blood glucose levels by 66.7% in diabetic mice at 0.01% in the diet for 3 days. Other exemplified substituted fused imidazole derivatives include the following:



Compound	R1	X	Formula
295983	OCH2CF3		C ₃₄ H ₃₇ F ₃ N ₂ O ₇
295984	4-F-PhCH2S		C ₃₉ H ₄₁ FN ₂ O ₆ S
295985	SPh		C ₃₈ H ₄₀ N ₂ O ₆ S
295986	4-F-PhCH2O	HCl	C ₃₉ H ₄₁ FN ₂ O ₇ ·HCl

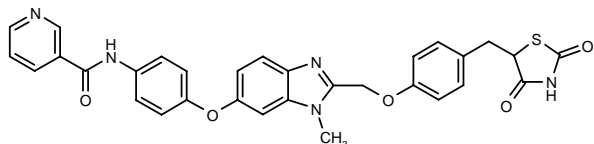
SOURCE – Sankyo.

REFERENCES

1. Fujita, T. et al. (Sankyo Co., Ltd.) *Substd. fused imidazole derivs.* JP 2000351777, WO 0061582.

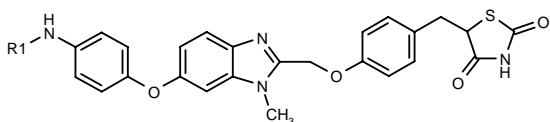
296079

N-[4-[2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenoxy-methyl]-1-methyl-1*H*-benzimidazol-6-yloxy]phenyl]pyr-idine-3-carboxamide



C31 H25 N5 O5 S; Mol wt: 579.6345

ACTION – Blood glucose-lowering agent, potentially useful for the treatment of diabetes, obesity, impaired glucose tolerance and related disorders. The compound lowered blood glucose levels by 63.6% in diabetic mice at 0.01% in the diet for 3 days. Other exemplified substituted fused imidazole derivatives include the following:



Compound	R1	Formula
296081	1-adamantyl-NHCO	C ₃₆ H ₃₇ N ₅ O ₅ S
296082	SO ₂ Me	C ₂₆ H ₂₄ N ₄ O ₆ S ₂

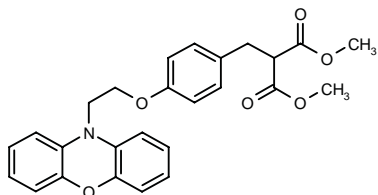
SOURCE – Sankyo.

REFERENCES

1. Fujita, T. et al. (Sankyo Co., Ltd.) *Amine derivs.* JP 2000351779, WO 0061581.

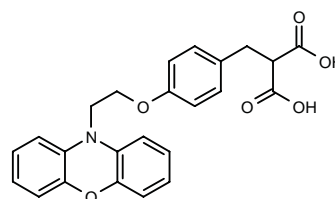
296200

2-[4-[2-(10*H*-Phenoxazin-10-yl)ethoxy]benzyl]malonic acid dimethyl ester



C26 H25 N O6; Mol wt: 447.4845

ACTION – Peroxisome proliferator-activated receptor PPAR α and PPAR γ activator with the ability to reduce blood glucose and triglyceride levels and thus potentially useful for the treatment of diabetes and obesity. Compound is also reported to decrease apoptosis in β -cells of islets of Langerhans. Another specifically claimed compound is:



296201: C₂₄ H₂₁ N O6

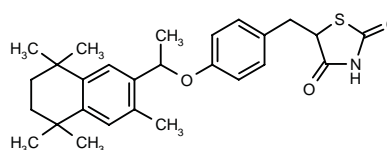
SOURCE – Novo Nordisk.

REFERENCES

1. Jeppesen, L. et al. (Novo Nordisk A/S) *New cpds., their preparation and use.* WO 0063190.

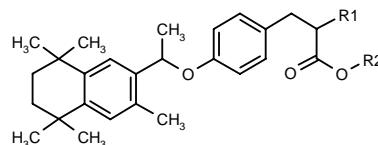
296202

5-[4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione



C27 H33 N O3 S; Mol wt: 451.6277

ACTION – Retinoid X receptor (RXR) and peroxisome proliferator-activated receptor PPAR α and PPAR γ activator reported to reduce blood glucose and triglyceride levels and thus potentially useful for the treatment of diabetes and obesity. Compound is also reported to decrease apoptosis in β -cells of islets of Langerhans. Other specifically claimed compounds are:



Compound	R1	R2	Formula
296204	OEt	Me	C ₂₉ H ₄₀ O ₄
296205	OEt	H	C ₂₈ H ₃₈ O ₄
296207	(S)-2-(PhCO)-PhNH	H	C ₃₉ H ₄₃ NO ₄

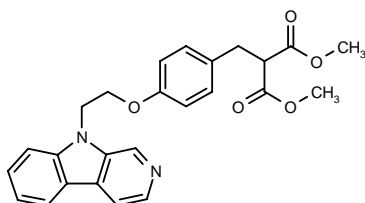
SOURCE – Novo Nordisk.

REFERENCES

1. Sauerberg, P. et al. (Novo Nordisk A/S) *New cpds., their preparation and use.* WO 0063196.

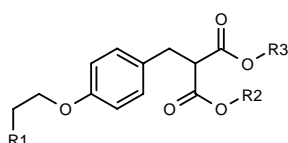
296208

2-[4-[2-(9*H*-Pyrido[3,4-*b*]indol-9-yl)ethoxy]benzyl]malonic acid dimethyl ester



C₂₅ H₂₄ N₂ O₅; Mol wt: 432.4736

ACTION – Peroxisome proliferator-activated receptor PPAR α and PPAR γ activator that reduces blood glucose and triglyceride levels and is thus potentially useful for the treatment of diabetes and obesity. Compound is also reported to decrease apoptosis in β -cells of islets of Langerhans. Other specifically claimed compounds are:



Compound	R1	R2=R3	Formula
296209	pyrido[3,4- <i>b</i>]indol-9-yl	H	C ₂₃ H ₂₀ N ₂ O ₅
296210	10,11-dihydro-5 <i>H</i> -dibenzo[<i>b,f</i>]azepin-5-yl	Me	C ₂₈ H ₂₉ NO ₅
296211	3-(3- <i>i</i> -Pr-5-isoxazolyl)-pyrido[3,4- <i>b</i>]indol-9-yl	Me	C ₃₁ H ₃₁ N ₃ O ₆

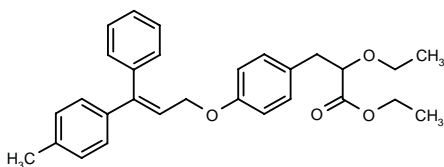
SOURCE – Novo Nordisk.

REFERENCES

1. Dörwald, F.Z. et al. (Novo Nordisk A/S;Boehringer Ingelheim GmbH) *Substd. imidazoles, their preparation and use*. WO 0063208.

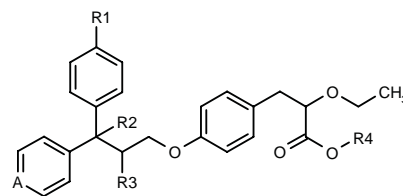
296212

2-Ethoxy-3-[4-[3-(4-methylphenyl)-3-phenyl-2-propenyl-oxy]phenyl]propionic acid ethyl ester



C₂₉ H₃₂ O₄; Mol wt: 444.5678

ACTION – Peroxisome proliferator-activated receptor PPAR α and PPAR γ activator that reduces blood glucose and triglyceride levels and is thus potentially useful for the treatment of diabetes and obesity. Compound is also reported to decrease apoptosis in β -cells of islets of Langerhans. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	A	Isomer	Formula
296213	H	H	H	Et	C(Me)		C ₂₉ H ₃₄ O ₄
296214	H	bond		Et	N		C ₂₇ H ₂₉ NO ₄
296216	Me	bond		Et	C(Me)	S	C ₃₀ H ₃₄ O ₄
296218	2-furyl	bond		H	C(2-furyl)	S	C ₃₄ H ₃₀ O ₆

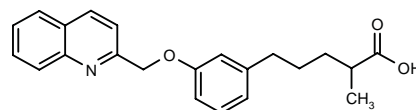
SOURCE – Novo Nordisk.

REFERENCES

1. Murray, A. et al. (Novo Nordisk A/S) *New cpds., their preparation and use*. WO 0063153.

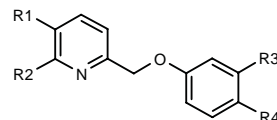
296482

2-Methyl-5-[3-(2-quinolinylmethoxy)phenyl]pentanoic acid

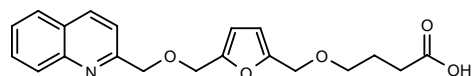


C₂₂ H₂₃ N O₃; Mol wt: 349.4277

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator, potentially useful in the treatment or prevention of diabetes, hyperinsulinemia, insulin resistance, hyperlipidemia, arteriosclerosis, hypertension and obesity. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	Formula
296483	Ph	H	2 <i>H</i> -tetrazol-5-yl-(CH ₂) ₃ O	H	C ₂₂ H ₂₁ N ₅ O ₂
296485	-CH=CHCH=CH-		CH ₂ CH(Me)CH ₂ -CH(Me)CO ₂ H	H	C ₂₃ H ₂₅ NO ₃
296486	-CH=CHCH=CH-		Me	5-tetrazolyl-(CH ₂) ₃ O	C ₂₁ H ₂₁ N ₅ O ₂
296487	-CH=CHCH=CH-		(CH ₂) ₄ CO ₂ H	H	C ₂₁ H ₂₁ NO ₃
296488	-CH=CHCH=CH-		(CH ₂) ₅ CO ₂ H	H	C ₂₂ H ₂₃ NO ₃



296484: C₂₀ H₂₁ N O₅

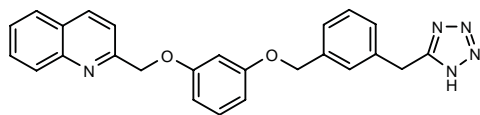
SOURCE – Aventis Pharma.

REFERENCES

1. Jayyosi, Z. et al. (Aventis Pharmaceuticals, Inc.) *Di-aryl acid derivs. as PPAR receptor ligands*. WO 0064888.

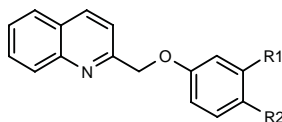
296490

2-[3-[3-(1*H*-Tetrazol-5-ylmethyl)benzyloxy]phenoxy-methyl]quinoline

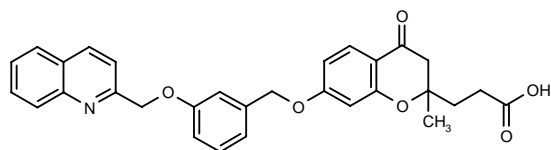


C₂₅ H₂₁ N₅ O₂; Mol wt: 423.4739

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator, potentially useful in the treatment or prevention of diabetes, hyperinsulinemia, insulin resistance, hyperlipidemia, arteriosclerosis, hypertension and obesity. Other specifically claimed compounds are:



Compound	R1	R2	Formula
296491	H	3-(5-tetrazolyl-CH ₂)-PhCH ₂ O	C ₂₅ H ₂₁ N ₅ O ₂
296492	2-CO ₂ H-3-Me-PhCH ₂ O	H	C ₂₅ H ₂₁ NO ₄



296493: C₃₀ H₂₇ N O₆

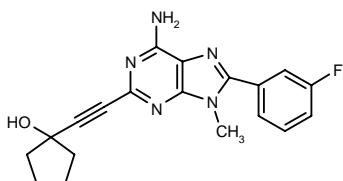
SOURCE – Aventis Pharma.

REFERENCES

1. Jayyosi, Z. et al. (Aventis Pharmaceuticals, Inc.) *Tri-aryl acid derivs. as PPAR receptor ligands*. WO 0064876.

298322

1-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9*H*-purin-2-yl]-ethynyl]cyclopentanol



C₁₉ H₁₈ F N₅ O; Mol wt: 351.3832

ACTION – Orally active hypoglycemic agent proven to inhibit NECA-induced glucose production in rat hepatocytes (IC₅₀ = 0.42 μM) and to significantly reduce blood glucose levels in KKA^y diabetic mice after oral administration (10-30 mg/kg), with greater potency than the reference compounds glibenclamide and metformin. Compound exhibited functional adenosine A_{2B} receptor-antagonist activity (IC₅₀ = 0.063 μM in CHO.K1 cells transfected with human A_{2B} receptors) but receptor binding studies indicated no selectivity relative to A_{2A} and A₁ receptors (K_i = 9.8 and 20 nM, respectively). Potentially useful for the treatment of type 2 diabetes.

SOURCE – Eisai.

REFERENCES

1. Asano, O. et al. (Eisai Co., Ltd.) *Purine derivs. and adenosine A₂ receptor antagonists serving as preventives/remedies for diabetes*. EP 1054012, JP 1999263789, WO 9935147.

2. Harada, H. et al. *2-Alkynyl-8-aryl-9-ethyladenines as novel adenosine receptor antagonists: Their synthesis and structure-activity relationships toward hepatic glucose production induced via agonism of the A_{2B} receptor*. J Med Chem 2001, 44(2): 170.

B1-T4-Ins

298944

1B-[O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosine]-30B-L-alanineinsulin (human)

N^αB¹-L-Thyroxyl-insulin

ACTION – Hepatoselective insulin analogue designed to restore the physiological balance of insulin following peripheral administration. After s.c. administration to healthy human subjects, compound was well tolerated and rapidly absorbed, showed a longer half-life and higher protein binding than NPH insulin and induced the same amount of hepatic glucose as NPH insulin, indicating equivalent hepatic potency. The analogue exhibited reduced peripheral effects compared to NPH insulin, had no effect on metabolic clearance of glucose and exhibited a reduced capacity to inhibit lipolysis.

SOURCES – Deutsches Wollforschungsinstitut, Aachen (DE); King's College London, London (GB).

REFERENCES

1. Jones, R.H. et al. (Deutsches Wollforschungsinstitut; King's College London) *Hepatoselective pharmaceutical actives*. US 5854208, US 6063761, WO 9505187.

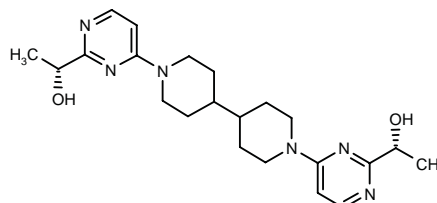
2. Shojaee Moradie, F. et al. *Novel hepatoselective insulin analog - Studies with a covalently linked thyroxyl-insulin complex in humans*. Diabetes Care 2000, 23(8): 1124.

3. Shojaee-Moeadie, F. et al. *Novel hepatoselective insulin analogues: Studies with covalently linked thyroxyl-insulin complexes*. Diabetic Med 1998, 15: 928.

TREATMENT OF DIABETIC COMPLICATIONS

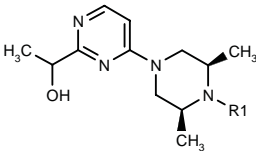
295491

1(*R*)-[4-[1-[2-[1(*R*)-Hydroxyethyl]pyrimidin-4-yl]piperidin-4-yl]piperidin-1-yl]pyrimidin-2-yl]ethan-1-ol

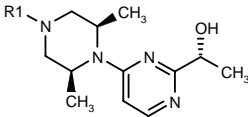


C₂₂ H₃₂ N₆ O₂; Mol wt: 412.5348

ACTION – Sorbitol dehydrogenase inhibitor with the ability to lower fructose levels and prevent diabetic complications, both alone and combined with a glycogen phosphorylase inhibitor. Combinations of this compound and an Na⁺/H⁺ exchange (NHE-1) inhibitor reduce tissue damage resulting from ischemia and are indicated for the prevention of perioperative myocardial ischemia. Other specifically claimed aminopyridines include the following:



Compound	R1	Isomer	Formula
295493	4-(MeOCH2)-6-Me-2-pyrimidinyl	R	C ₁₉ H ₂₈ N ₆ O ₂
295494	2-(4-Me-1-imidazolyl)-4-pyrimidinyl	R	C ₂₀ H ₂₆ N ₈ O
295495	4-MeO-6-i-PrO-1,3,5-triazin-2-yl	R	C ₁₉ H ₂₉ N ₇ O ₃
295496	2-[(R)-MeCH(OH)]-4-pyrimidinyl	R	C ₁₈ H ₂₈ N ₆ O ₂
295498	2-[MeCH(OH)]-4-pyrimidinyl		C ₁₈ H ₂₈ N ₆ O ₂
295500	2-[(R)-MeCH(OH)]-4-pyrimidinyl	S	C ₁₈ H ₂₈ N ₆ O ₂



Compound	R1	Formula
295492	imidazo[1,2-a]pyridin-2-yl-CO	C ₂₀ H ₂₄ N ₆ O ₂
295499	4-MeO-6-(MeOCH2)-1,3,5-triazin-2-yl	C ₁₈ H ₂₇ N ₇ O ₃

SOURCE – Pfizer.

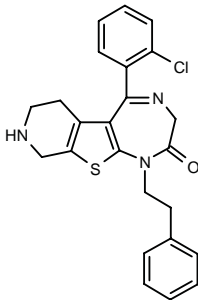
REFERENCES

1. Chu-Moyer, M.Y. et al. (Pfizer Products Inc.) *Aminopyrimidines as sorbitol dehydrogenase inhibitors*. WO 0059510.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

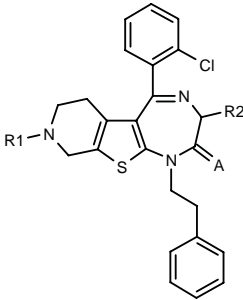
295782

5-(2-Chlorophenyl)-1-(2-phenylethyl)-2,3,6,7,8,9-hexahydro-1*H*-pyrido[4',3':4,5]thieno[2,3-*e*][1,4]diazepin-2-one

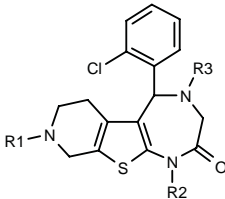


C24 H22 Cl N3 O S; Mol wt: 435.9768

ACTION – Somatostatin receptor modulator with potential in the treatment of a broad range of disorders involving somatostatin receptors such as acromegaly, hypophysial adenoma, diabetes, gastric acid secretion, peptic ulcers, irritable bowel syndrome, cancer and fibrosis. Other exemplified compounds from this series of pyrido-thieno-diazepines include the following:



Compound	R1	R2	A	Formula
295783	4-MeO-2-NO2- -PhNHCS	H	O	C ₃₂ H ₂₈ ClN ₅ O ₄ S ₂
295784	H	H	S	C ₂₄ H ₂₂ ClN ₃ S ₂
295785	4-MeO-2-NO2- -PhNHCS	H	S	C ₃₂ H ₂₈ ClN ₅ O ₃ S ₃
295786	H	OH	O	C ₂₄ H ₂₂ ClN ₃ O ₂ S
295787	4-MeO-2-NO2- -PhNHCS	OH	O	C ₃₂ H ₂₈ ClN ₅ O ₅ S ₂
295788	H	OCO- (CH2)6NH2	O	C ₃₁ H ₃₅ ClN ₄ O ₃ S
295789	4-MeO-2-NO2- -PhNHCS	OCO- (CH2)6NH2	O	C ₃₉ H ₄₁ ClN ₆ O ₆ S ₂



Compound	R1	R2	R3	Formula
295790	H	CH2CH2Ph	CO(CH2)6- NH2	C ₃₁ H ₃₇ ClN ₄ O ₂ S
295791	4-MeO-2-NO2- -PhNHCS	CH2CH2Ph	CO(CH2)6- NH2	C ₃₉ H ₄₃ ClN ₆ O ₅ S ₂
295792	H	CH2CH2Ph	CH2CH=C(Me)2	C ₂₉ H ₃₂ ClN ₃ OS
295793	4-MeO-2-NO2- -PhNHCS	CH2CH2Ph	CH2CH=C(Me)2	C ₃₇ H ₃₈ ClN ₅ O ₄ S ₂
295795	H	CH2CH2Ph	H	C ₂₄ H ₂₄ ClN ₃ OS
295796	4-MeO-2-NO2- -PhNHCS	CH(Me)Pr	H	C ₂₉ H ₃₂ ClN ₅ O ₄ S ₂

SOURCE – SCRAS.

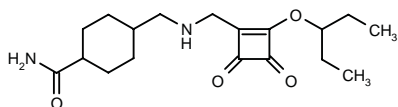
REFERENCES

1. Liberatore, A.-M. and Bigg, D. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Pyrido-thieno-diazepines, method for the production thereof and pharmaceutical compsns. containing said pyrido-thieno-diazepines*. FR 2791980, WO 0061587.

TREATMENT OF MALE SEXUAL DYSFUNCTION

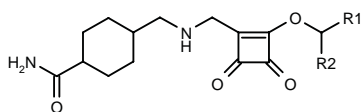
296274

4-[2-(1-Ethylpropoxy)-3,4-dioxo-1-cyclobuten-1-ylmethyl-aminomethyl]cyclohexanecarboxamide



C18 H28 N2 O4; Mol wt: 336.4292

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor with potential in the treatment of benign prostatic hypertrophy, incontinence, dysmenorrhea, erectile dysfunction and other male and female sexual dysfunctions, angina pectoris, pulmonary hypertension, apoplexy, arteriosclerosis, ventricular insufficiency, peripheral vascular disorders, asthma, bronchitis, allergic rhinitis, glaucoma and intestinal motility disorders. Other specifically claimed compounds from this series of 2-alkoxy-cyclobutene-3,4-dione derivatives are:



Compound	R1	R2	Formula
296275	Pr	Pr	C ₂₀ H ₃₂ N ₂ O ₄
296276	H	H	C ₁₄ H ₂₀ N ₂ O ₄
296278	Me	Me	C ₁₆ H ₂₄ N ₂ O ₄
296280	H	Me	C ₁₅ H ₂₂ N ₂ O ₄
296282	H	cyclopropyl	C ₁₇ H ₂₄ N ₂ O ₄
296283	H	cyclohexyl	C ₂₀ H ₃₀ N ₂ O ₄
296284	Et	cyclohexyl	C ₂₂ H ₃₄ N ₂ O ₄
296285	H	Ph	C ₂₀ H ₂₄ N ₂ O ₄
296286	H	cyclopentyl	C ₁₉ H ₂₈ N ₂ O ₄
296287	H	cyclopentyl-CH2	C ₂₀ H ₃₀ N ₂ O ₄

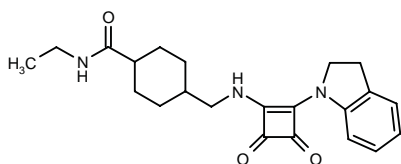
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Bovy, P.R. et al. (Sanofi-Synthélabo) *2-Alkoxy-cyclobutene-3,4-dione derivs., preparation and therapeutic use thereof*. FR 2792634, WO 0063160.

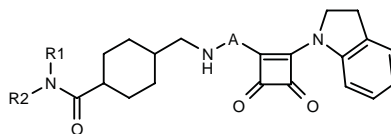
296289

4-[2-(2,3-Dihydro-1H-indol-1-yl)-3,4-dioxo-1-cyclobuten-1-ylaminomethyl]-N-ethylcyclohexanecarboxamide

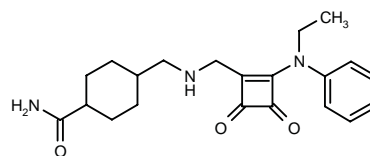


C22 H27 N3 O3; Mol wt: 381.4733

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor with potential in the treatment of benign prostatic hypertrophy, urinary incontinence, dysmenorrhea, erectile dysfunction and other male and female sexual dysfunctions, angina pectoris, pulmonary hypertension, stroke, arteriosclerosis, ventricular insufficiency, peripheral vascular disorders, asthma, bronchitis, allergic rhinitis, glaucoma and intestinal motility disorders. Other specifically claimed compounds from this series of cyclobutene-3,4-dione derivatives are:



Compound	R1	R2	A	Formula
296291	Me	H	bond	C ₂₁ H ₂₅ N ₃ O ₃
296301	4i-Pr	H	bond	C ₂₃ H ₂₉ N ₃ O ₃
296302	cyclopropyl-CH2	H	bond	C ₂₄ H ₂₉ N ₃ O ₃
296304	cyclopropyl	H	bond	C ₂₃ H ₂₇ N ₃ O ₃
296305	Et	Et	bond	C ₂₄ H ₃₁ N ₃ O ₃
296306	H	H	bond	C ₂₀ H ₂₃ N ₃ O ₃
296307	H	H	CH2	C ₂₁ H ₂₅ N ₃ O ₃



296310: C21 H27 N3 O3

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Bovy, P.R. and Philipppo, C. (Sanofi-Synthélabo) *Cyclobutene-3,4-dione derivs. as inhibitors of phosphodiesterase 5*. FR 2792635, WO 0063170.

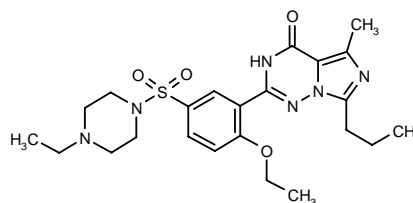
VARDENAFIL*

Prop INN

276900

2-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one

Bay-38-9456



C23 H32 N6 O4 S; Mol wt: 488.6098

ACTION – Agent for the treatment of male sexual dysfunction, a potent and selective phosphodiesterase type 5 (PDE5) inhibitor ($IC_{50} = 0.7$ nM vs > 100 nM for other PDE isozymes). In rabbit corpus cavernosum, compound produced concentration-dependent increases in cGMP levels that were potentiated in the presence of the nitric oxide (NO) donor sodium nitroprusside, cAMP levels being unaltered. Compound given i.v. (0.1-3 mg/kg) to conscious rabbits induced penile erections in a dose-dependent fashion and its effect was potentiated by concurrent administration of sodium nitroprusside and suppressed in the presence of the NO synthase inhibitor L-NAME. In clinical trials, vardenafil given orally (10-80 mg) to either healthy volunteers or patients with erectile dysfunction was safe and well tolerated; erectile response was similar at 20 mg and 40 mg. Compound showed rapid absorption ($t_{max} = 0.6$ -0.9 h) and an elimination half-life of 3-5 h. Currently in phase III trials.

SOURCE – Bayer.

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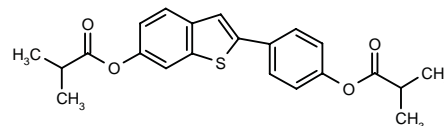
MONOGRAPH – Sorbera, L.A. et al. Vardenafil. Drugs Fut 2001, 26(2): 0141.

*Identified compound **276900** (see **276895**) Drug Data Rep 1999, 021(07): 0621.

TREATMENT OF GYNECOLOGICAL DISORDERS

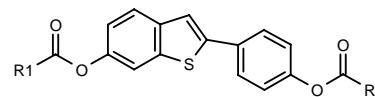
295477

2-Methylpropionic acid 4-[6-(2-methylpropionyloxy)benzo-thien-2-yl]phenyl ester



C22 H22 O4 S; Mol wt: 382.4778

ACTION – Estrogenic compound, a selective agonist at the estrogen ER β receptor, as demonstrated in CHO cells stably cotransfected with the rat oxytocin promoter, the luciferase reporter gene and the human estrogen ER α or ER β receptor. Potentially useful for the treatment of disorders related with estrogen deficiency such as peri- and postmenopausal complaints and osteoporosis. Other exemplified compounds are:



Compound	R1=R2	Formula
295478	i-Bu	C ₂₄ H ₂₆ O ₄ S
295479	t-Bu	C ₂₄ H ₂₆ O ₄ S
295480	Pr	C ₂₂ H ₂₂ O ₄ S
295481	OPr	C ₂₂ H ₂₂ O ₆ S

SOURCE – Akzo Nobel.

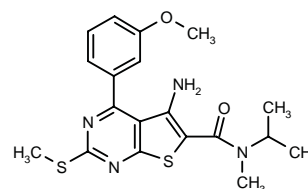
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AGENTS FOR FEMALE INFERTILITY

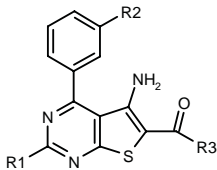
295808

5-Amino-N-isopropyl-4-(3-methoxyphenyl)-N-methyl-2-(methylsulfanyl)thieno[2,3-d]pyrimidine-6-carboxamide



C19 H22 N4 O2 S2; Mol wt: 402.5408

ACTION – Luteinizing hormone (LH) receptor agonist for use in the control of fertility, proven to stimulate LH-mediated testosterone production in murine testicular Leydig cells with an EC₅₀ value of 0.87 μM. *In vivo*, compound was shown to induce ovulation in follicle-stimulating hormone (FSH)-stimulated immature female mice at 50 mg/kg p.o. (50% ovulating animals). Other exemplified compounds from this series of bicyclic heteroaromatic derivatives include the following:



Compound	R1	R2	R3	Formula
295809	SMe	NHCOPh	t-BuNH	C ₂₆ H ₂₅ N ₅ O ₂ S ₂
295810	SMe	OMe	t-BuNH	C ₁₉ H ₂₂ N ₄ O ₂ S ₂
295811	OEt	OMe	t-BuNH	C ₂₀ H ₂₄ N ₄ O ₃ S
295812	2-thienyl	OMe	4-morpholinyl	C ₂₂ H ₂₀ N ₄ O ₃ S ₂
295813	SMe	t-BuNHCH ₂ CONH	t-BuNH	C ₂₄ H ₃₂ N ₆ O ₂ S ₂
295814	SMe	3-Pyr-(CH ₂) ₃ O	t-BuNH	C ₂₆ H ₂₉ N ₅ O ₂ S ₂

SOURCE – Akzo Nobel.

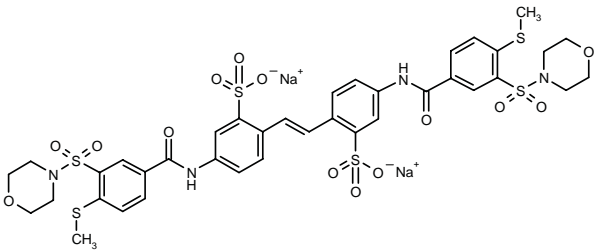
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CONTRACEPTIVES

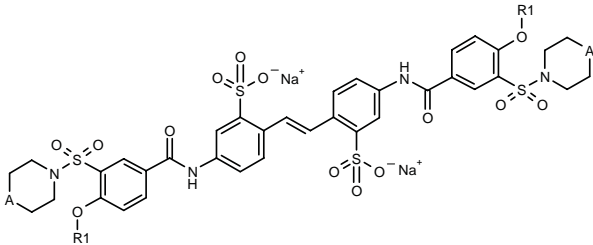
292801

4,4'-Bis[4-(methylsulfanyl)-3-(4-morpholinylsulfonyl)-benzamido]stilbene-2,2'-disulfonic acid disodium salt



C38 H38 N4 Na2 O14 S6; Mol wt: 1013.1080

ACTION – Follicle-stimulating hormone (FSH) antagonist with respective IC₅₀ values of 1.2 and 1.3 μM for binding affinity at the FSH receptor and functional antagonism of FSH-stimulated cAMP production. Potentially useful as a male or female contraceptive agent. Other related (bis)-stilbene sulfonic acid analogues include the following:



Compound	R1	A	Formula
292802	Me	SO2	C ₃₈ H ₃₈ N ₄ Na ₂ O ₁₈ S ₆
292803	Me	N(CHO)	C ₄₀ H ₄₀ N ₆ Na ₂ O ₁₆ S ₄
292804	CH ₂ CH ₂ OMe	O	C ₄₂ H ₄₆ N ₄ Na ₂ O ₁₈ S ₄
292805	4-THP	O	C ₄₆ H ₅₀ N ₄ Na ₂ O ₁₈ S ₄

SOURCE – American Home Products.

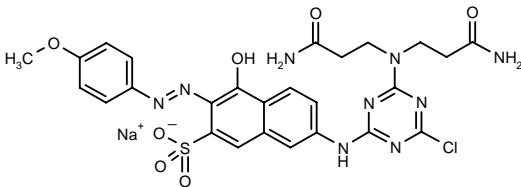
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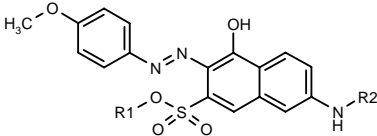
295358

7-[4-[Bis(3-amino-3-oxopropyl)amino]-6-chloro-1,3,5-triazin-2-ylamino]-4-hydroxy-3-[2-(4-methoxyphenyl)diazeryl]naphthalene-2-sulfonic acid sodium salt



C26 H25 Cl N9 Na O7 S; Mol wt: 666.0485

ACTION – Follicle-stimulating hormone (FSH) antagonist, potentially useful as a male and female contraceptive. Compound inhibited the binding of [¹²⁵I]-hFSH to the hFSH receptor cloned in CHO cells with an IC₅₀ value of 5.0 μM. In addition, it was shown to inhibit hFSH-induced cAMP accumulation in CHO-3D2 cells (IC₅₀ = 1.4 μM), as well as hFSH-induced estradiol secretion in primary cultures of rat granulosa cells (IC₅₀ = 1.9 μM). Other specifically claimed compounds from this series of 7-amino-4-hydroxy-3-(4-methoxyphenylazo)naphthalene-2-sulfonic acid derivatives are:



Compound	R1	R2	Formula
295359	Na	4-[N(CH ₂ CH ₂ OH) ₂]-6-Cl-1,3,5-triazin-2-yl	C ₂₄ H ₂₃ ClN ₇ NaO ₇ S
295360	Na	4-N(Me)2-PhCO	C ₂₆ H ₂₃ N ₄ NaO ₆ S
295361	H	3,5-(MeO)2-PhCO	C ₂₆ H ₂₃ N ₃ O ₆ S
295362	H	COPh	C ₂₄ H ₁₉ N ₃ O ₆ S
295363	H	2,6-(MeO)2-PhCO	C ₂₆ H ₂₃ N ₃ O ₆ S
295365	H	3,4-(MeO)2-PhCO	C ₂₆ H ₂₃ N ₃ O ₆ S

SOURCE – American Home Products.

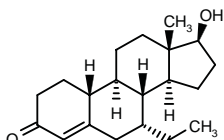
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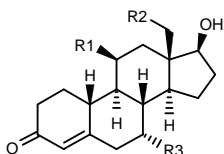
295482

7 α -Ethyl-17 β -hydroxyestra-4-en-3-one



C₂₀H₃₀O₂; Mol wt: 302.4550

ACTION – Orally active androgen shown to suppress serum luteinizing hormone (LH) in mature castrated male rats with an ED₅₀ of 2.5 mg/kg p.o. Its half-life was 48 min in human hepatocytes after incubation with 10 nM. Potentially useful as a male contraceptive and in male or female hormone replacement therapy. Other exemplified 7 α -19-nortestosterone derivatives are:



Compound	R1	R2	R3	Formula
295483	H	H	vinyl	C ₂₀ H ₂₈ O ₂
295484	Me	H	Et	C ₂₁ H ₃₂ O ₂
295485	Me	H	vinyl	C ₂₁ H ₃₀ O ₂
295486	H	H	CH=CHMe	C ₂₁ H ₃₀ O ₂
295487	H	H	cyclopropyl	C ₂₁ H ₃₀ O ₂
295488	H	Me	Et	C ₂₁ H ₃₂ O ₂
295489	H	Me	vinyl	C ₂₁ H ₃₀ O ₂

SOURCE – Akzo Nobel.

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DROSPIRENONE/ETHINYLESTRADIOL

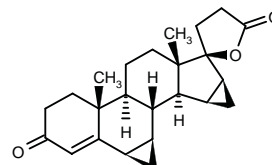
New combination

296543

Drospirenone

169995

6 β ,7 β :15 β ,16 β -Dimethylene-3-oxo-17 α -preg-4-ene-21,17-carbolactone

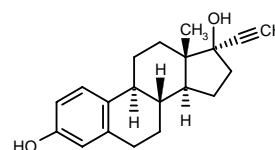


C₂₄H₃₀O₃; Mol wt: 366.4980

Ethinylestradiol

125559

17 α -Ethinylestradiol



C₂₀H₂₄O₂; Mol wt: 296.4130

ACTION – Oral female contraceptive containing the progestogen drospirenone and the estrogen ethinylestradiol. Drospirenone also possesses antimineralocorticoid and antiandrogenic properties similar to natural progestogens.

INDICATION – Prevention of pregnancy.

PRESENTATION – Tablets containing 3 mg of drospirenone and 30 μ g of ethinylestradiol in a 21-day regimen.

PROPRIETARY NAME – Yasmin (DE).

SOURCE – Schering AG.

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16. *Drospirenone-containing contraceptive first launched in Germany.* DailyDrugNews.com (Daily Essentials) 2001, Jan 22.

17. *Schering AG provides update at annual press conference.* DailyDrugNews.com (Daily Essentials) 2001, March 30.

18. *Schering AG's Yasmin approved in The Netherlands.* DailyDrugNews.com (Daily Essentials) 2000, June 5.

19. *Schering AG's Yasmin receives European-wide approval.* DailyDrugNews.com (Daily Essentials) 2000, Aug 30.

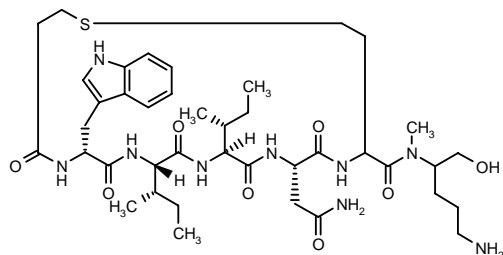
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UTERINE STIMULANTS AND TOCOLYTICS

296101

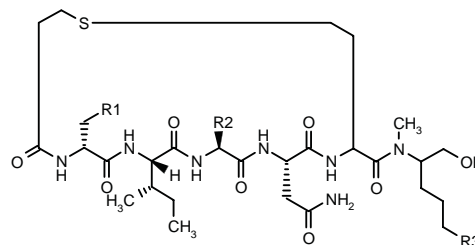
3-Sulfanylpropionyl-D-tryptophyl-L-isoleucyl-L-alloisoleucyl-L-asparaginyl-2-aminobutyryl-N-methyl-DL-ornithinol S-3.1-C-4.6-sulfide



C40 H63 N9 O8 S; Mol wt: 830.0587

ACTION – Oxytocin receptor antagonist, as demonstrated by a K_i value of 0.25 ± 0.16 nM against [125 I]-oxytocin binding to cloned human oxytocin receptors and an IC_{50} value of 5 ± 1 nM for inhibition of oxytocin-induced contractions of uterine muscle tissue from women in late pregnancy undergoing cesarean section, reported to possess improved stability in aqueous media. In addition, compound was also shown to inhibit oxytocin-induced uterine contractions *in vivo* in rats. Potentially useful for

decreasing or blocking uterine muscle contraction associated with preterm labor and menstrual pain. Other specifically claimed peptides from this series of heptapeptide oxytocin analogues are:



Compound	R1	R2	R3	Formula
296102	3-indolyl	(R)-CH(Me)Et	CH ₂ NH ₂	C ₄₁ H ₆₅ N ₉ O ₈ S
296103	3-indolyl	(R)-CH(Me)Et	NHC(=NH)NH ₂	C ₄₁ H ₆₅ N ₁₁ O ₈ S
296104	2-Naph	CH(Et) ₂	NH ₂	C ₄₃ H ₆₆ N ₉ O ₈ S
296105	2-Naph	(R)-CH(Me)Et	NH ₂	C ₄₂ H ₆₄ N ₉ O ₈ S

SOURCE – Ferring.

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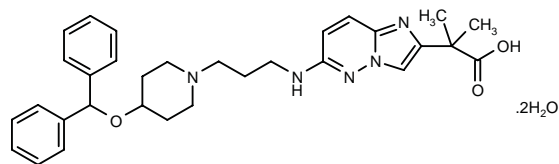
DERMATOLOGIC DRUGS

TREATMENT FOR ALLERGIC SKIN DISORDERS

TAK-427

296945

2-[6-[3-[4-(Diphenylmethoxy)piperidin-1-yl]propylamino]imidazo[1,2-*b*]pyridazin-2-yl]-2-methylpropionic acid dihydrate



C31 H37 N5 O3 . 2H₂O; Mol wt: 563.6949

ACTION – Eosinophil infiltration inhibitor with anti-histaminic activity, potentially useful for the treatment of atopic dermatitis. In *ex vivo* binding studies, compound showed little effect on central H₁ receptors and in a guinea pig model of eczema-type dermatitis, orally administered compound (1 and 10 mg/kg) diminished both symptoms associated with dermatitis and eosinophil number in the dermis.

SOURCE – Takeda.

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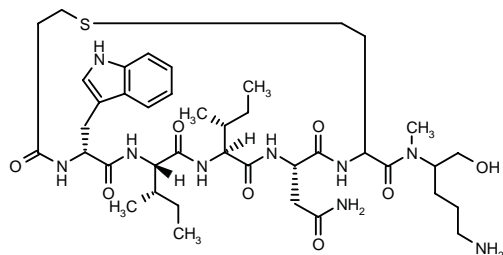
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UTERINE STIMULANTS AND TOCOLYTICS

296101

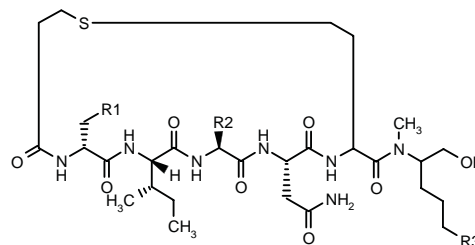
3-Sulfanylpropionyl-D-tryptophyl-L-isoleucyl-L-alloisoleucyl-L-asparaginyl-2-aminobutyryl-N-methyl-DL-ornithinol S-3.1-C-4.6-sulfide



C40 H63 N9 O8 S; Mol wt: 830.0587

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296103	3-indolyl	(R)-CH(Me)Et	NHC(=NH)NH ₂	C ₄₁ H ₆₅ N ₁₁ O ₈ S
296104	2-Naph	CH(Et) ₂	NH ₂	C ₄₃ H ₆₆ N ₉ O ₈ S
296105	2-Naph	(R)-CH(Me)Et	NH ₂	C ₄₂ H ₆₄ N ₉ O ₈ S

SOURCE – Ferring.

REFERENCES

1. Melin, P. et al. (Ferring BV Group Holding) *Heptapeptide oxytocin analogues.* US 6143722, WO 9823636.

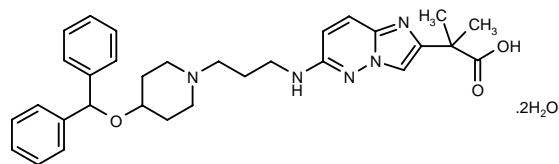
DERMATOLOGIC DRUGS

TREATMENT FOR ALLERGIC SKIN DISORDERS

TAK-427

296945

2-[6-[3-[4-(Diphenylmethoxy)piperidin-1-yl]propylamino]-imidazo[1,2-*b*]pyridazin-2-yl]-2-methylpropionic acid dihydrate



C31 H37 N5 O3 . 2H₂O; Mol wt: 563.6949

ACTION – Eosinophil infiltration inhibitor with anti-histaminic activity, potentially useful for the treatment of atopic dermatitis. In *ex vivo* binding studies, compound showed little effect on central H₁ receptors and in a guinea pig model of eczema-type dermatitis, orally administered compound (1 and 10 mg/kg) diminished both symptoms associated with dermatitis and eosinophil number in the dermis.

SOURCE – Takeda.

REFERENCES

1. Kawano, Y. et al. (Takeda Chemical Industries, Ltd.) *Condensed pyridazine derivs., their production and use.* EP 0979231, JP 1999310581, JP 1999310582, WO 9849167.

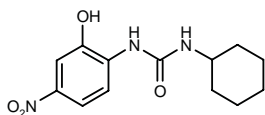
2. Kawano, Y. et al. (Takeda Chemical Industries, Ltd.) *Fused pyridazine derivs., process for the preparation of the same and uses thereof*. JP 2000191664, JP 2000198735, WO 0023450.

3. Gyoten, M. et al. *Synthetic studies on eosinophil infiltration inhibitors with antihistaminic activity*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 2P-19.

ANTIPSORIATICS

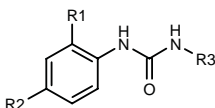
295367

N-Cyclohexyl-*N'*-(2-hydroxy-4-nitrophenyl)urea



C13 H17 N3 O4; Mol wt: 279.2943

ACTION – IL-8 receptor (CXCR1/CXCR2) antagonist for the treatment of disorders characterized by excessive or unregulated IL-8 production including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft-vs.-host disease, Alzheimer's disease, allograft rejection, malaria, restenosis and angiogenesis. The compound is reported to be able to inhibit the binding of a chemokine such as IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-7 to the CXCR1 or CXCR2 receptor. A representative compound from a series of phenyl ureas, where the following compounds are also included:



Compound	R1	R2	R3	Formula
295368	OH	NO2	allyl	C ₁₀ H ₁₁ N ₃ O ₄
295369	OH	NO2	t-Bu	C ₁₁ H ₁₅ N ₃ O ₄
295370	OH	NO2	CH ₂ CH ₂ CO ₂ Et	C ₁₂ H ₁₅ N ₃ O ₆
295371	OH	NO2	i-Pr	C ₁₀ H ₁₃ N ₃ O ₄
295372	OH	NO2	CH ₂ CH(OMe) ₂	C ₁₁ H ₁₅ N ₃ O ₆
295373	OH	NO2	CH ₂ CH ₂ OMe	C ₁₀ H ₁₃ N ₃ O ₅
295374	OH	NO2	CH ₂ CH(Me)OCH ₂ Ph	C ₁₇ H ₁₉ N ₃ O ₅
295375	OH	NO2	C(Me) ₂ OMe	C ₁₁ H ₁₅ N ₃ O ₅
295376	OH	NO2	i-PrCH(CHO)	C ₁₂ H ₁₅ N ₃ O ₅
295377	OH	NO2	CH(Me)CH(Me)OCH ₂ Ph	C ₁₈ H ₂₁ N ₃ O ₅
295378	NHSO ₂ Ph	CN	i-Pr	C ₁₇ H ₁₈ N ₄ O ₃ S

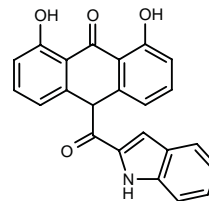
SOURCE – GlaxoSmithKline.

REFERENCES

1. Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. JP 2000514049, US 6133319, WO 9749680.

298501

1,8-Dihydroxy-10-(1*H*-indol-2-ylcarbonyl)anthracen-9(10*H*)-one



C23 H15 N O4; Mol wt: 369.3745

ACTION – Derivative of the antipsoriatic anthralin that retains the same excellent antiproliferative activity and ability to induce the differentiation of keratinocytes, but a reduced capability to induce hydroxyl radicals and consequently associated with less damage to keratinocyte membranes.

SOURCES – Universität Regensburg, Regensburg (DE); Westfälische Wilhelms-Universität Münster, Münster (DE).

REFERENCES

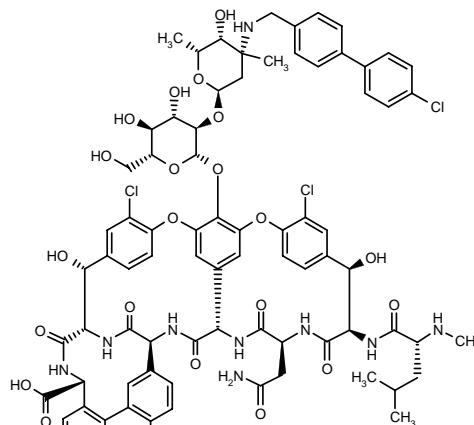
1. Müller, K. et al. *Heterocyclic substituted anthralin derivatives as inhibitors of keratinocyte growth and inducers of differentiation*. Bioorg Med Chem Lett 2001, 11(1): 47.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

295535^{1,2}

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-3-(Carbamoylmethyl)-10-chloro-44-[2-*O*-[3-(4'-chlorobiphenyl-4-ylmethylamino)-3-*C*-methyl-2,3,6-trideoxy- α -L-galactopyranosyl]- β -D-glucopyranosyloxy]-7,22,28,30,32-pentahydroxy-6-(*N*-methyl-D-leucylamino)-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclopentacosine-26-carboxylic acid



C79 H84 Cl3 N9 O24; Mol wt: 1649.9310

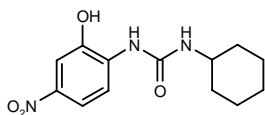
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ANTIPSORIATICS

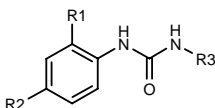
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295378	NHSO ₂ Ph	CN	i-Pr	C ₁₇ H ₁₈ N ₄ O ₃ S

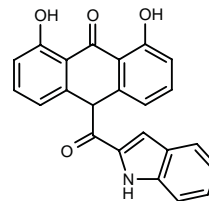
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SOURCES – Universität Regensburg, Regensburg (DE); Westfälische Wilhelms-Universität Münster, Münster (DE).

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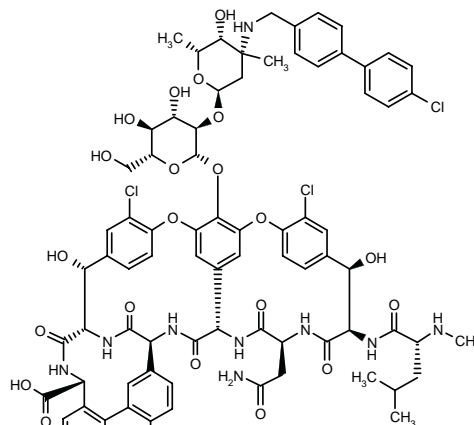
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ANTIINFECTIVE THERAPY

ANTIBIOTICS

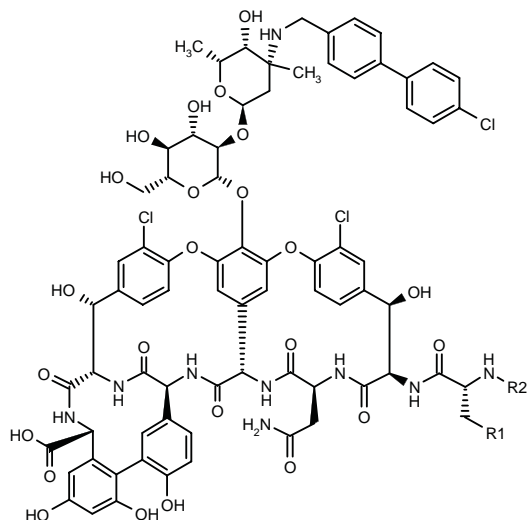
295535^{1,2}

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C79 H84 Cl3 N9 O24; Mol wt: 1649.9310

ACTION – Glycopeptide antibiotic active against Gram-positive and Gram-negative bacteria such as *Enterococcus faecium* ATCC 49624, *E. faecium* CL 4931, *Enterococcus faecalis* ATCC 29212, *E. faecalis* CL 4877, *Staphylococcus aureus* ATCC 29213 and *S. aureus* ATCC 33591 (MIC = 0.031, 6.25, 0.12, 6.25, 0.25 and 0.12 µg/ml, respectively). Other exemplified glycopeptides include the following:



Compound	R1	R2	Formula
295537	CONH2	CO2Et	C ₇₉ H ₈₁ Cl ₃ N ₁₀ O ₂₇
295539	Et	H	C ₇₇ H ₈₀ Cl ₃ N ₉ O ₂₄

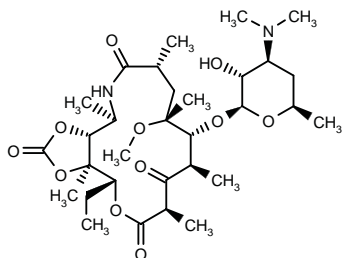
SOURCES – Incara; Princeton University, Princeton, NJ (US).

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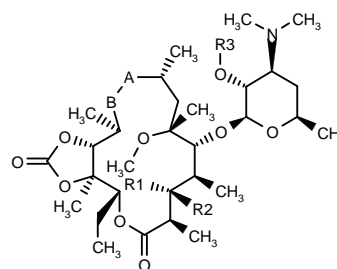
296311

3-Des(hexopyranosyloxy)-3-oxo-6-O-methyl-9a-aza-9a-homoerythromycin A 11,12-cyclic carbonate



C31 H52 N2 O11; Mol wt: 628.7548

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria, a representative compound from a series of 6-O-methyl-erythromycin A 8a- and 9a-lactams, wherein the following compounds are also exemplified:



Compound	R1	R2	R3	A	B	Formula
296312	H	2,6-dideoxy-3-C,3-O-(Me)2- α -L-ribohexopyranosyl-O	H	CO	NH	C ₃₉ H ₆₈ N ₂ O ₁₄
296317	H	OH	Ac	CO	NH	C ₃₃ H ₅₆ N ₂ O ₁₂
296319	H	4-NO ₂ -PhCH ₂ COO	H	CO	NH	C ₃₉ H ₅₉ N ₃ O ₁₄
296320	H	OH	H	CO	NH	C ₃₁ H ₅₄ N ₂ O ₁₁
296323	H	4-NO ₂ -PhCH ₂ COO	H	NH	CO	C ₃₉ H ₅₉ N ₃ O ₁₄
296325		-O-	H	NH	CO	C ₃₁ H ₅₂ N ₂ O ₁₁

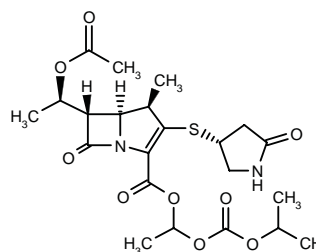
SOURCE – Pliva.

REFERENCES

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296594

(1*R*,5*S*,6*S*)-6-[1(*R*)-Acetoxyethyl]-1-methyl-2-[5-oxopyrrolidin-3(*R*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid 1-(isopropoxycarbonyloxy)ethyl ester



C22 H30 N2 O9 S; Mol wt: 498.5500

ACTION – Carbapenem antibiotic with good oral bioavailability (58.4%) in dogs.

SOURCE – Sankyo.

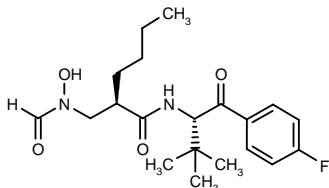
REFERENCES

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ANTIBACTERIAL DRUGS

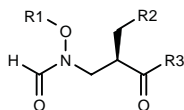
296036

N-[1(*S*)-(4-Fluorobenzoyl)-2,2-dimethylpropyl]-2(*R*)-(N-formyl-*N*-hydroxyaminomethyl)hexanamide



C₂₀ H₂₉ F N₂ O₄; Mol wt: 380.4571

ACTION – Antibacterial agent that is believed to act by inhibiting bacterial polypeptide deformylase (PDF) and is active against both Gram-positive and Gram-negative organisms. Other compounds from this series of hydroxamic acid and *N*-formylhydroxylamine derivatives are:



Compound	R1	R2	R3	Formula
296037	H	cyclopentyl	(S)-4-MeO-PhCOCH(t-Bu)NH	C ₂₃ H ₃₄ N ₂ O ₅
296038	CH ₂ Ph	Pr	(F)5-PhO	C ₂₁ H ₂₀ F ₅ NO ₄
296039	H	Pr	(S)-2-Pyr-CH ₂ COCH(t-Bu)NH	C ₂₀ H ₃₁ N ₃ O ₄
296040	H	Pr	(S)-4-NH ₂ -PhCOCH(t-Bu)NH	C ₂₀ H ₃₁ N ₃ O ₄
296041	H	Pr	(S)-4-(4-PhCH ₂ -1-Piz)-PhCOCH(t-Bu)NH	C ₃₁ H ₄₄ N ₄ O ₄
296042	H	Pr	(S)-4-N(Pr)2-PhCOCH(t-Bu)NH	C ₂₆ H ₄₃ N ₃ O ₄
296043	H	Pr	(S)-t-BuCH(Ac)NH	C ₁₅ H ₂₈ N ₂ O ₄

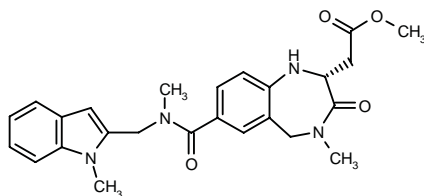
SOURCE – British Biotech.

REFERENCES

1. Todd, R.S. et al. (British Biotech Pharmaceuticals Ltd.) *Antimicrobial agents*. WO 0061134.

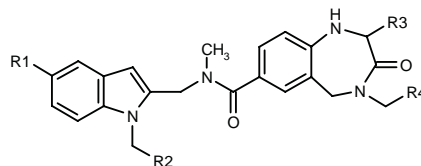
296409

2-[4-Methyl-7-[*N*-methyl-*N*-(1-methyl-1*H*-indol-2-yl-methyl)carbamoyl]-3-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-2(*R*)-yl]acetic acid methyl ester



C₂₅ H₂₈ N₄ O₄; Mol wt: 448.5202

ACTION – Antibacterial agent that inhibits Fab I (previously known as EnvM), an enzyme that is essential to bacterial fatty acid biosynthesis. This compound is useful for the treatment of bacterial infections and may also be of use as an antifungal agent and in combinations with other antibiotics. Other specifically claimed tetrahydro-1,4-benzodiazepin-3-one derivatives are:



Compound	R1	R2	R3	R4	Isomer	Formula
296410	H	H	CH ₂ CO ₂ Me	H	2S	C ₂₅ H ₂₈ N ₄ O ₄
296411	H	H	Me	H	2R	C ₂₃ H ₂₆ N ₄ O ₂
296412	H	H	CH ₂ Ph	H	2R	C ₂₉ H ₃₀ N ₄ O ₂
296413	H	4-OH-Ph	CH ₂ CO ₂ Me	H	2R	C ₃₁ H ₃₂ N ₄ O ₅
296414	H	4-OH-Ph	Me	H	2R	C ₂₉ H ₃₀ N ₄ O ₃
296415	H	H	CH ₂ OH	H	2R	C ₂₃ H ₂₆ N ₄ O ₃
296416	H	H	H	H		C ₂₂ H ₂₄ N ₄ O ₂
296417	H	4-OH-Ph	CH ₂ OH	H	2R	C ₂₉ H ₃₀ N ₄ O ₄
296418	OCH ₂ Ph	H	CH ₂ OH	H	2R	C ₃₀ H ₃₂ N ₄ O ₄
296419	OH	H	CH ₂ OH	H	2R	C ₂₃ H ₂₆ N ₄ O ₄
296420	H	H	Pr	H	2R	C ₂₅ H ₃₀ N ₄ O ₂
296421	H	H	CH ₂ OH	Ph	2R	C ₂₉ H ₃₀ N ₄ O ₃
296422	H	H	CH ₂ OH	CH ₂ Ph	2R	C ₃₀ H ₃₂ N ₄ O ₃

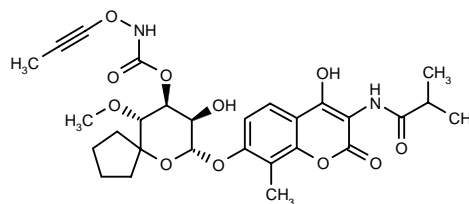
SOURCE – GlaxoSmithKline.

REFERENCES

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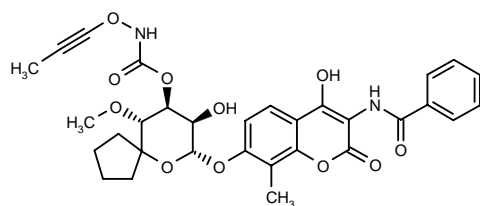
296501

N-(1-Propynyloxy)carbamic acid 8(*R*)-hydroxy-7(*R*)-[4-hydroxy-8-methyl-3-(2-methylpropionamido)-2-oxo-2*H*-1-benzopyran-7-yloxy]-10(*R*)-methoxy-6-oxaspiro[4.5]dec-9(*S*)-yl ester



C₂₈ H₃₄ N₂ O₁₁; Mol wt: 574.5796

ACTION – Antibacterial agent particularly active against anaerobic Gram-positive bacteria that acts by inhibiting DNA gyrase B. It exhibited MIC values in the range 0.04-0.63 µg/ml against *Staphylococcus aureus* 011HT18, *Staphylococcus epidermidis* 0126042, coagulase-negative *Staphylococcus* 012HT5, *Streptococcus pyogenes* 02A1UC1, *Streptococcus pneumoniae* 030BI2, *Enterococcus faecium* 02D3IP2 and *Enterococcus faecalis* 02D2UC5. Another specifically claimed ribose-substituted aromatic amide is:



296502: C31 H32 N2 O11

SOURCE – Aventis Pharma.

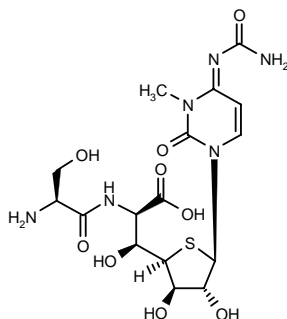
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SB-217452

298004

1-[4-(Carbamoylimino)-1,2,3,4-tetrahydro-3-methyl-2,4-dioxypyrimidin-1-yl]-1,6-dideoxy-6-(L-serylamino)-4-thio-D-glycero-β-D-allo-heptofuranuronic acid



C16 H24 N6 O9 S; Mol wt: 476.4646

ACTION – Potent inhibitor of seryl-tRNA synthetase (serine-tRNA ligase) isolated from *Streptomyces* sp. ATCC 700974, able to inhibit both rat and *Staphylococcus aureus* enzymes with IC₅₀ values of approximately 8 nM. Compound, however, showed only weak antibacterial activity against a limited range of microorganisms including *S. aureus*, *Escherichia coli*, *Moraxella catarrhalis* and *Streptococcus pyogenes* (MIC = 256, 256, 8 and 16 µg/ml, respectively).

SOURCE – GlaxoSmithKline.

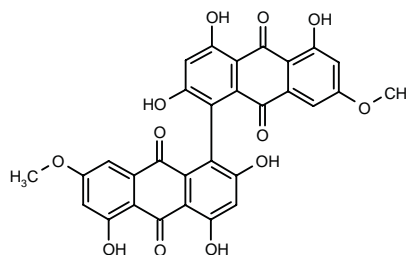
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YM-187787

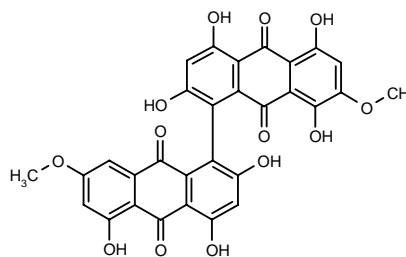
296600

1,1'-Bis(2,4,5-trihydroxy-7-methoxy-9,10-anthraquinone)



C30 H18 O12; Mol wt: 570.4602

ACTION – Antibacterial agent isolated from *Verticillium lecanii* Q57371 (FERM P-17197), active *in vitro* against *Staphylococcus aureus* FDA209P and *Bacillus subtilis* ATCC6633. Another compound isolated from the same source is:



YM-187781 [296603]: C30 H18 O13

SOURCE – Yamanouchi.

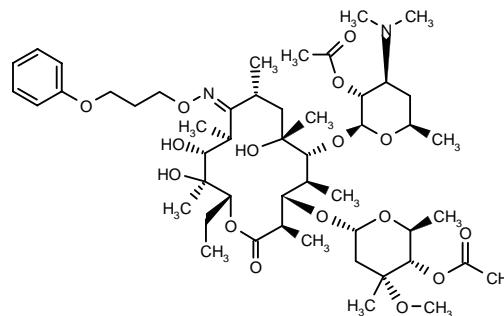
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ANTIMYCOBACTERIAL AGENTS

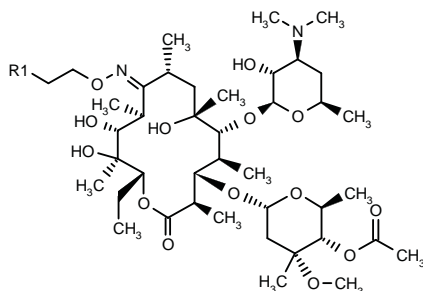
295960

2',4''-O-Diacetylerythromycin A 9-[O-(3-phenoxypropyl)-oxime]



C50 H82 N2 O16; Mol wt: 967.1958

ACTION – Antimycobacterial agent with potent activity against *Mycobacterium avium* and *Mycobacterium intracellulare* strains such as *M. avium* 20092 (MIC = 0.78 µg/ml vs. > 50 and 50 µg/ml, respectively, for clarithromycin and rifampicin) and *M. intracellulare* 20067 (MIC = 0.39 µg/ml vs. 1.56 and 1.56 µg/ml, respectively, for clarithromycin and rifampicin). Within this series of erythromycin derivatives, the following compounds are also included:



Compound	R1	Formula
295961	CH ₂ OPh	C ₄₈ H ₈₀ N ₂ O ₁₅
295962	C ₆ H ₁₃	C ₄₇ H ₈₆ N ₂ O ₁₄
295963	cyclohexyl	C ₄₇ H ₈₄ N ₂ O ₁₄

SOURCE – Hokuriku.

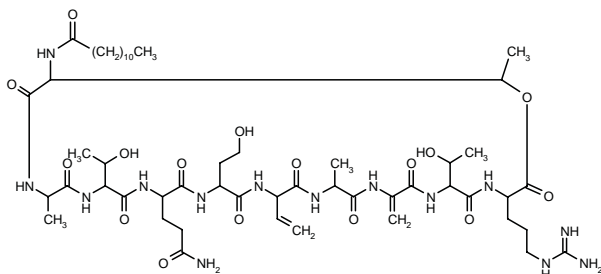
REFERENCES

1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *Erythromycin derivs.* JP 2000351794, WO 0061593.

ANTIFUNGAL AGENTS

296435

N-[21-(3-Amino-3-oxopropyl)-3-(3-guanidinopropyl)-6,2-bis(1-hydroxyethyl)-18-(2-hydroxyethyl)-12,27,31-trimethyl-9-methylene-2,5,8,11,14,17,20,23,26,29-decaoxo-15-vinyl-1-oxa-4,7,10,13,16,19,22,25,28-nonaazacyclohexatriacontan-20-yl]dodecanamide



C52 H88 N14 O16; Mol wt: 1165.3490

ACTION – Antifungal depsidecapeptide isolated from the bacterium *Pseudomonas syringae* that does not contain chlorothreonine, which is believed to cause irritation at the injection site of formulations containing pseudomycin compounds. The compound gave respective MIC values of 10, 10, 1.25 and 20 µg/ml against *Candida albicans*, *Candida parapsilosis*, *Cryptococcus neoformans* and *Histoplasma capsulatum*, respectively.

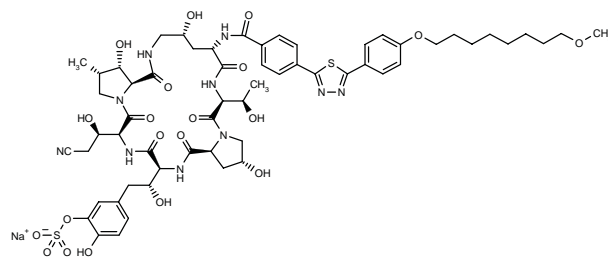
SOURCE – Lilly.

REFERENCES

1. Kulanthaivel, P. et al. (Eli Lilly and Company) *Antifungal agents isolated from Pseudomonas syringae*. WO 0063240.

296459

(2*R*,6*S*,9*S*,11*R*,14*aS*,15*R*,16*S*,20*S*,23*S*,25*aS*)-20-[2-Cyano-1(*R*)-hydroxyethyl]-23-[1(*S*),2(*S*)-dihydroxy-2-[4-hydroxy-3-(sulfooxy)phenyl]ethyl]-2,11,15-trihydroxy-6-[1(*R*)-hydroxyethyl]-9-[4-[5-[4-(8-methoxyoctyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]benzamido]-16-methyl-perhydrodipyrrolo[2,1-*c*:2',1'- η][1,4,7,10,13,16]hexaazacycloheicosine-5,8,14,19,22,25-hexaone sodium salt



C59 H75 N10 Na O20 S2; Mol wt: 1331.4130

ACTION – Antifungal cyclic hexapeptide active against a variety of fungi including *Aspergillus*, *Cryptococcus*, *Candida*, *Mucor*, *Actinomyces*, *Histoplasma*, dermatophytes, *Malassezia* and *Fusarium* spp., and expected to be useful for the treatment and prevention of *Pneumocystis carinii* pneumonia. The compound was active against *Candida albicans* FP-633 (MIC < 0.3 µg/ml). Other exemplified polypeptides include the following:

SOURCE – Fujisawa.

REFERENCES

1. Tojo, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Cyclic hexapeptides having antibiotic activity*. WO 0064927.

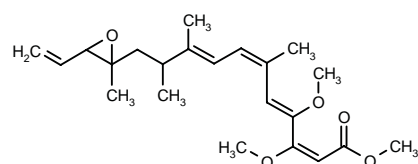
HALIANGICIN

296597

3,4-Dimethoxy-6,9,10-trimethyl-11-(2-methyl-3-vinyloxiran-2-yl)-2(*E*),4(*Z*),6(*Z*),8(*E*)-undecatetraenoic acid methyl ester

12,13-Epoxy-3,4-dimethoxy-6,9,10,12-tetramethyl-2(*E*),4(*Z*),6(*Z*),8(*E*)-pentadecapentaenoic acid methyl ester

SMP-2



C22 H32 O5; Mol wt: 376.4898

ACTION – Antifungal agent isolated from the culture of the marine myxobacterium *Haliangium luteum*, with MIC values of 6.3, 12.5, 50 and 12.5 µg/ml, respectively, against *Aspergillus fumigatus* AJ-117190, *Aspergillus niger* AJ-117374, *Candida albicans* AJ-5682 and *Mucor hiemalis* AJ-117396. A representative compound from a series of polyene antibiotics.

SOURCE – Ajinomoto.

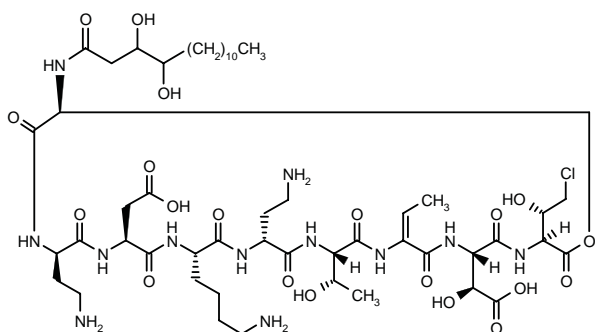
REFERENCES

1. Fudou, R. et al. (Ajinomoto Co., Inc.) *Novel polyenes antibiotics*. JP 2000239266.
2. Fudou, R. et al. *Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium*. 1. *Fermentation and biological characteristics*. J Antibiot 2001, 54(2): 149.
3. Fudou, R. et al. *Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium*. 2. *Isolation and structural elucidation*. J Antibiot 2001, 54(2): 153.

PSEUDOMYCIN A'

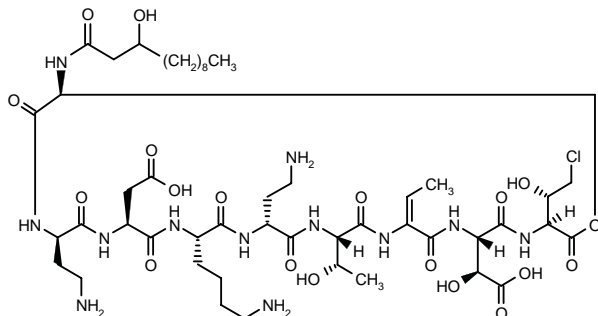
296433

N-(3,4-Dihydroxypentadecanoyl)-L-seryl-D-2,4-diaminobutanoyl-L-aspartyl-L-lysyl-L-2,4-diaminobutanoyl-L-allothreonyl-2,3-didehydro-2-aminobutanoyl-3(*S*)-hydroxy-L-aspartyl-4-chloro-L-threonine C-1.9-*O*-2.1-lactone



C52 H89 Cl N12 O20; Mol wt: 1237.7920

ACTION – Antifungal depsinonapeptide isolated from the bacterium *Pseudomonas syringae*, proven active against *Candida albicans*, *Candida parapsilosis*, *Cryptococcus neoformans* and *Histoplasma capsulatum* (MIC = 2.5, 5.0, 1.25 and 5.0 µg/ml, respectively). Potentially useful for the treatment of systemic fungal infections or fungal skin infections. Another pseudomycin from the same source is:



Pseudomycin B' [296434]: C49 H83 Cl N12 O19

SOURCE – Lilly.

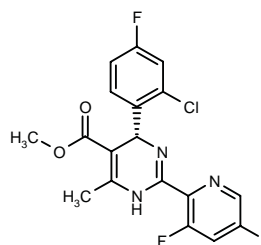
REFERENCES

1. Kulanthaivel, P. et al. (Eli Lilly and Company) *Pseudomycin natural products*. WO 0063237.

ANTIVIRAL DRUGS

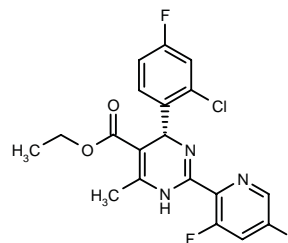
295321

4(*R*)-(2-Chloro-4-fluorophenyl)-2-(3,5-difluoropyridin-2-yl)-6-methyl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester



C18 H13 Cl F3 N3 O2; Mol wt: 395.7667

ACTION – Antiviral agent for the treatment of acute or chronic hepatitis B virus infections. Another specifically claimed compound from this series of dihydropyrimidines is:



295323: C19 H15 Cl F3 N3 O2

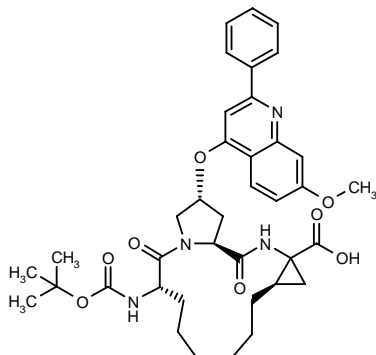
SOURCE – Bayer.

REFERENCES

1. Stölting, J. et al. (Bayer AG) *Dihydropyrimidines and their use in the treatment of hepatitis B*. WO 0058302.

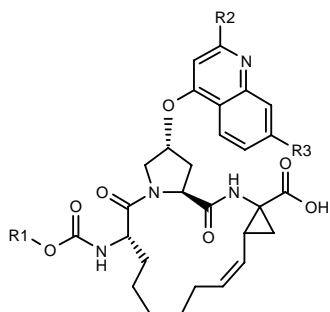
295540

(2*R*,6*S*,12*aR*,15*aS*)-6-(*tert*-Butoxycarbonylamino)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,15-dioxohexadecahydro-13*aH*-cyclopropa[*e*]pyrrolo[1,2-*a*][1,4]-diazacyclotetradecine-13*a*-carboxylic acid

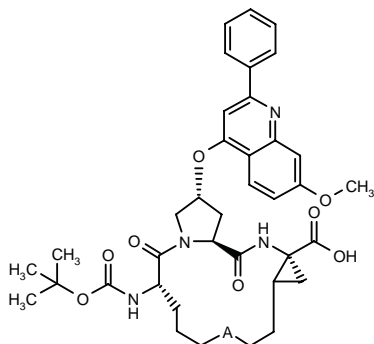


C₃₈ H₄₆ N₄ O₈; Mol wt: 686.8014

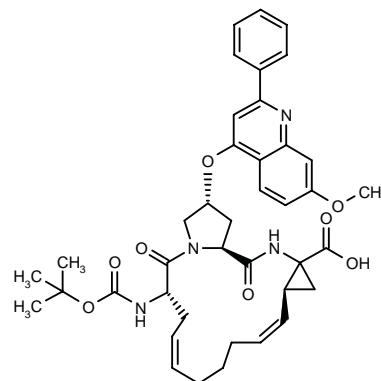
ACTION – Macrocyclic peptide active against hepatitis C virus (HCV) that works by selectively inhibiting NS3 protease, being devoid of significant inhibitory activity against other serine proteases such as human leukocyte elastase, porcine pancreatic elastase or bovine pancreatic chymotrypsin, or cysteine proteases such as human liver cathepsin B. The compound is active against both major genotypes of HCV found in clinical isolates. Other exemplified compounds include the following:



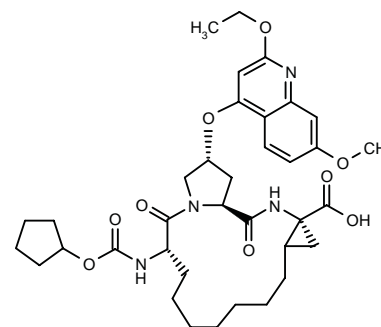
Compound	R1	R2	R3	Isomer	Formula
295549	t-Bu	H	H	S	C ₃₂ H ₄₀ N ₄ O ₇
295557	t-Bu	2-(AcNH)-4-thiazolyl	N(Me)2		C ₃₉ H ₄₉ N ₇ O ₈ S
295558	t-Bu	2-(AcNH)-4-thiazolyl	OMe		C ₃₈ H ₄₆ N ₆ O ₈ S
295560	cyclobutyl	2-(AcNH)-4-thiazolyl	OMe		C ₃₈ H ₄₄ N ₆ O ₈ S



Compound	A	Isomer	Formula
295555	-CH=CH-	R	C ₃₉ H ₄₆ N ₄ O ₈
295556	-OCH ₂ -		C ₃₈ H ₄₆ N ₄ O ₉



295553: C₄₀ H₄₆ N₄ O₈



295561: C₃₆ H₄₈ N₄ O₉

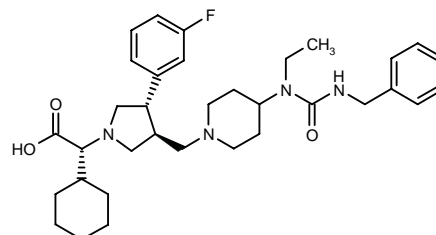
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Tsantrizos, Y.S. et al. (Boehringer Ingelheim [Canada] Ltd.) *Macrocyclic peptides active against the hepatitis C virus*. WO 0059929.

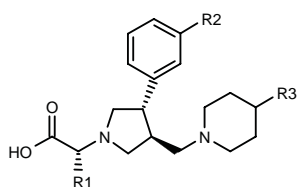
AIDS MEDICINES**295738**

2(*R*)-[3(*S*)-[4-(3-Benzyl-1-ethylureido)piperidin-1-ylmethyl]-4(*S*)-(3-fluorophenyl)pyrrolidin-1-yl]-2-cyclohexylacetic acid



C₃₄ H₄₇ F N₄ O₃; Mol wt: 578.7683

ACTION – Agent for the treatment and prevention of HIV infection and AIDS, as well as for the treatment of inflammatory and immune disorders such as asthma, allergic rhinitis, dermatitis, conjunctivitis, rheumatoid arthritis and atherosclerosis, with the ability to modulate the activity of chemokine receptors, particularly CCR3 and/or CCR5 receptors. Other exemplified compounds from this series of pyrrolidine derivatives include the following:



Compound	R1	R2	R3	Formula
295739	cyclohexyl	F	4-F-PhCH ₂ NHCON(Et)	C ₃₄ H ₄₆ F ₂ N ₄ O ₃
295740	i-Pr	H	3,4-(F)2-PhCH ₂ NHCON(Et)	C ₃₁ H ₄₂ F ₂ N ₄ O ₃
295742	cyclohexyl	F	CONHCH ₂ Ph	C ₃₂ H ₄₂ FN ₃ O ₄
295743	cyclohexyl	H	4-CN-PhCH ₂ NHCON(Me)	C ₃₄ H ₄₅ N ₅ O ₃
295745	cyclohexyl	H	4-Cl-PhCH ₂ NHCOCH ₂	C ₃₃ H ₄₄ ClN ₃ O ₃
295746	cyclohexyl	H	4-CN-PhCH ₂ NHCOO	C ₃₃ H ₄₂ N ₄ O ₄
295747	cyclohexyl	H	4-CN-PhCH ₂ NHCONH	C ₃₃ H ₄₃ N ₅ O ₃

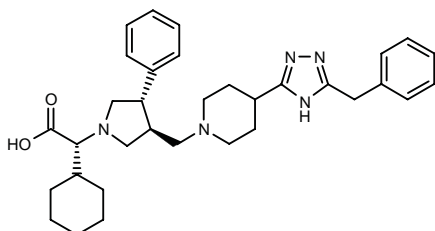
SOURCE – Merck & Co.

REFERENCES

1. Berk, S. et al. (Merck & Co., Inc.) *Pyrrolidine modulators of chemokine receptor activity*. WO 0059497.

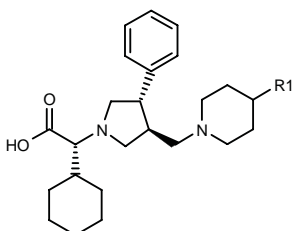
295749

2(R)-[3(S)-[4-(5-Benzyl-4H-1,2,4-triazol-3-yl)piperidin-1-ylmethyl]-4(S)-phenylpyrrolidin-1-yl]-2-cyclohexylacetic acid

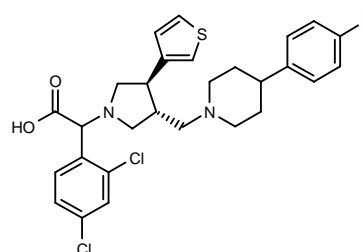


C₃₃ H₄₃ N₅ O₂; Mol wt: 541.7357

ACTION – Agent for the treatment and prevention of HIV infection and AIDS, as well as for the treatment of inflammatory and immune disorders such as asthma, allergic rhinitis, dermatitis, conjunctivitis, rheumatoid arthritis and atherosclerosis, with the ability to modulate the activity of chemokine receptors, particularly CCR3 and/or CCR5 receptors. Other exemplified compounds from this series of pyrrolidine derivatives include the following:



Compound	R1	Formula
295750	4-F-Ph	C ₃₀ H ₃₉ FN ₂ O ₂
295751	3-Me-5-Ph-1-pyrazolyl	C ₃₄ H ₄₄ N ₄ O ₂
295752	1-Et-5-(PhCH ₂)-3-pyrazolyl	C ₃₆ H ₄₈ N ₄ O ₂
295756	1-Me-3-(PhCH ₂)-5-pyrazolyl	C ₃₅ H ₄₆ N ₄ O ₂
295757	1-Et-4-(PhCH ₂)-3-pyrazolyl	C ₃₆ H ₄₈ N ₄ O ₂
295758	5-Ph-4H-1,2,4-triazol-3-yl	C ₃₂ H ₄₁ N ₅ O ₂



295754: C₂₈ H₂₉ Cl₂ F N₂ O₂ S

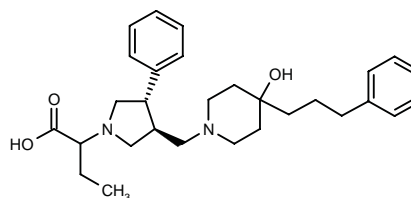
SOURCE – Merck & Co.

REFERENCES

1. Chapman, K. et al. (Merck & Co., Inc.) *Pyrrolidine modulators of chemokine receptor activity*. WO 0059502.

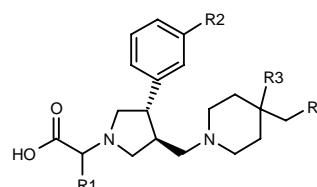
295759

2-[3(S)-[4-Hydroxy-4-(3-phenylpropyl)piperidin-1-ylmethyl]-4(S)-phenylpyrrolidin-1-yl]butyric acid



C₂₉ H₄₀ N₂ O₃; Mol wt: 464.6460

ACTION – Agent for the treatment and prevention of HIV infection and AIDS, as well as for the treatment of inflammatory and immune disorders such as asthma, allergic rhinitis, dermatitis, conjunctivitis, rheumatoid arthritis and atherosclerosis, with the ability to modulate the activity of chemokine receptors, particularly CCR3 and/or CCR5 receptors. Other exemplified compounds from this series of pyrrolidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
295760	3-indolyl	H	OH	CH ₂ CH ₂ Ph	C ₃₆ H ₄₁ N ₃ O ₃
295761	(R)-cyclohexyl	H	H	CH=CHPh	C ₃₃ H ₄₄ N ₂ O ₂
295762	(R)-i-Pr	H	H	2,1,3-benzoxa-diazol-5-yl-CH ₂ CH ₂	C ₃₀ H ₄₀ N ₄ O ₃
295763	(R)-i-Pr	F	H	2,1,3-benzoxa-diazol-5-yl-CH ₂ CH ₂	C ₃₀ H ₃₉ FN ₄ O ₃
295764	(S)-cyclobutyl-CH ₂	H	H	2-CN-PhCH ₂ CH ₂	C ₃₃ H ₄₃ N ₃ O ₂
295765	(S)-i-Pr	F	H	3-CN-4-F-Ph-CH ₂ CH ₂	C ₃₁ H ₃₉ F ₂ N ₃ O ₂
295766	(R)-cyclobutyl-CH ₂	F	H	3,5-(CF ₃) ₂ -Ph-CH ₂ CH ₂	C ₃₄ H ₄₁ F ₇ N ₂ O ₂

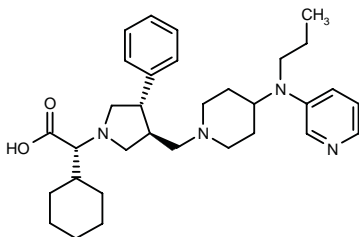
SOURCE – Merck & Co.

REFERENCES

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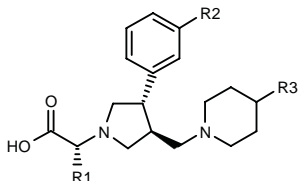
295767

2(*R*)-Cyclohexyl-2-[3(*S*)-phenyl-4(*S*)-[4-[*N*-propyl-*N*-(3-pyridyl)amino]piperidin-1-ylmethyl]pyrrolidin-1-yl]acetic acid



C32 H46 N4 O2; Mol wt: 518.7414

ACTION – Agent for the treatment and prevention of HIV infection and AIDS, as well as for the treatment of inflammatory and immune disorders such as asthma, allergic rhinitis, dermatitis, conjunctivitis, rheumatoid arthritis and atherosclerosis, with the ability to modulate the activity of chemokine receptors, particularly CCR3 and/or CCR5 receptors. Other exemplified compounds from this series of pyrrolidine derivatives include the following:



Compound	R1	R2	R3	Formula
295768	cyclohexyl	H	2-benzoxazolyl-N(Pr)	C ₃₄ H ₄₆ N ₄ O ₃
295769	cyclohexyl	H	5-Me-1,2,4-oxadiazol-3-yl-N(CH ₂ CH ₂ Ph)	C ₃₅ H ₄₇ N ₅ O ₃
295770	cyclobutyl-CH ₂	F	2-pyrimidinyl-N(CH ₂ -cyclopropyl)	C ₃₁ H ₄₂ FN ₅ O ₂
295771	cyclobutyl-CH ₂	F	4-F-PhSCH ₂ CH ₂	C ₃₁ H ₄₀ F ₂ N ₂ O ₂ S
295772	cyclohexyl	H	2,1,3-benzoxadiazol-5-yl-OCH ₂ CH ₂	C ₃₂ H ₄₂ N ₄ O ₄
295773	cyclohexyl	H	2-pyrazinyl-N(Et)	C ₃₀ H ₄₃ N ₅ O ₂

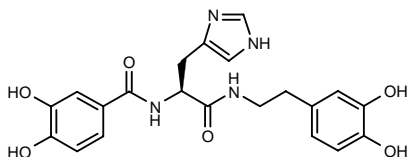
SOURCE – Merck & Co.

REFERENCES

1. Caldwell, C. et al. (Merck & Co., Inc.) *Pyrrolidine modulators of chemokine receptor activity*. WO 0059498.

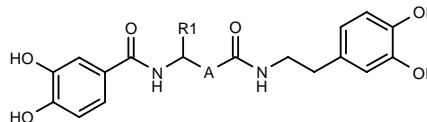
295774

*N*²-(3,4-Dihydroxybenzoyl)-*N*¹-[2-(3,4-dihydroxyphenyl)-ethyl]-L-histidinamide



C21 H22 N4 O6; Mol wt: 426.4268

ACTION – Antiviral agent for AIDS, an inhibitor of HIV-1 integrase (IC₅₀ = 0.1 μM). Other exemplified compounds from this series of hydroxyphenyl derivatives include the following:



Compound	R1	A	Formula
295775	3-F-4-OH-PhCH ₂	bond	C ₂₄ H ₂₃ FN ₂ O ₇
295776	(<i>S</i>)-CO ₂ CH ₂ Ph	-(CH ₂) ₂ -	C ₂₇ H ₂₈ N ₂ O ₈
295777	3-OH-PhCH ₂	bond	C ₂₄ H ₂₄ N ₂ O ₇

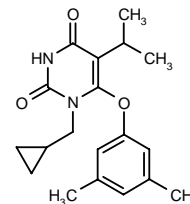
SOURCE – Pharmacor.

REFERENCES

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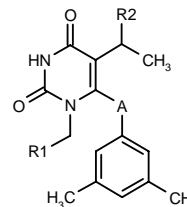
296019

1-(Cyclopropylmethyl)-5-isopropyl-6-(3,5-dimethylphenoxy)pyrimidine-2,4(1*H*,3*H*)-dione



C19 H24 N2 O3; Mol wt: 328.4096

ACTION – Antiviral pyrimidinedione derivative with potent anti-HIV activity and very low toxicity, as demonstrated by an EC₅₀ of 0.2 ng/ml for inhibition of HIV-induced cytopathic effect in MT-4 cells versus a cytotoxic CC₅₀ of 12.70 μg/ml in uninfected MT-4 cells (selectivity index > 635,000). Other exemplified compounds are:



Compound	R1	R2	A	Formula
296020	cyclopropyl	Me	S	C ₁₉ H ₂₄ N ₂ O ₂ S
296021	cyclobutyl	H	CO	C ₂₀ H ₂₄ N ₂ O ₃
296022	2-CN-Ph	Me	CO	C ₂₄ H ₂₃ N ₃ O ₃
296023	2,5-(F) ₂ -Ph	H	CO	C ₂₂ H ₂₀ F ₂ N ₂ O ₃
296024	Ac	Me	O	C ₁₈ H ₂₂ N ₂ O ₄

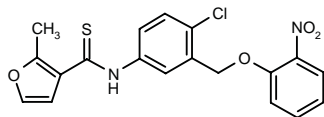
SOURCE – Samjin.

REFERENCES

1. Cho, E.-H. et al. (Samjin Pharmaceutical Co., Ltd.) *Antiviral pyrimidinedione derivs. and process for the preparation thereof*. WO 0061563, WO 0061564.

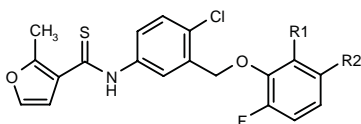
296083

N-[4-Chloro-3-(2-nitrophenoxy)methyl]phenyl]-2-methylfuran-3-carbothioamide



C₁₉ H₁₅ Cl N₂ O₄ S; Mol wt: 402.8565

ACTION – Anti-HIV agent giving EC₅₀ values of 27.1-39.3 nM against HIV-1_{IIIB} and EC₅₀ values of 0.0023, 0.08, 0.0075, 0.0045 and 0.0041 µg/ml against wild-type and 100-Ile, 138-Lys, 184-Ile and 184-Val mutant HIV-1 reverse transcriptase strains, respectively, as evaluated by inhibition of syncytium formation in infected CEM cells. Other exemplified compounds from this series of *N*-arylmethylthioanilide derivatives include the following:



Compound	R1	R2	Formula
296084	F	H	C ₁₉ H ₁₄ ClF ₂ NO ₂ S
296085	OMe	H	C ₂₀ H ₁₇ ClFNO ₃ S
296086	F	F	C ₁₉ H ₁₃ ClF ₃ NO ₂ S

SOURCE – Uniroyal.

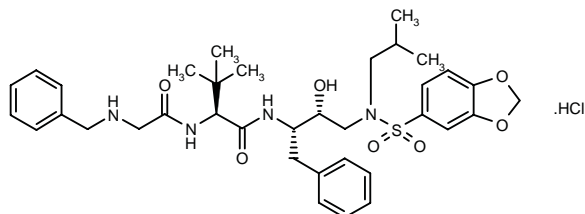
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296130

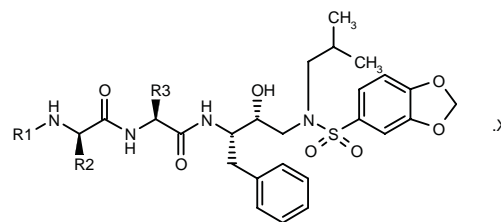
N-[3-[*N*-(1,3-Benzodioxol-5-ylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-hydroxypropyl]-2(*S*)-[2-(benzylamino)-acetamido]-3,3-dimethylbutyramide hydrochloride

N-Benzylglycyl-*N*¹-[3-[*N*-(1,3-benzodioxol-5-ylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-hydroxypropyl]-3-methyl-L-valinamide hydrochloride



C₃₆ H₄₈ N₄ O₇ S · HCl; Mol wt: 717.3231

ACTION – Anti-HIV agent, an HIV protease inhibitor (IC₅₀ = 2 nM) with antiviral efficacy in HIV-infected CEM cells (EC₅₀ = 24 nM). Other exemplified bis-amino acid hydroxyethylaminosulfonamide derivatives include the following:



Compound	R1	R2	R3	X	Formula
296133	Me	H	t-Bu		C ₃₀ H ₄₄ N ₄ O ₇ S
296134	Me	H	CH(Me)Et		C ₃₀ H ₄₄ N ₄ O ₇ S
296135	CH ₂ CH ₂ OH	H	t-Bu	HCl	C ₃₁ H ₄₆ N ₄ O ₈ S.HCl
296138	CH ₂ CH ₂ OMe	H	t-Bu	HCl	C ₃₂ H ₄₈ N ₄ O ₈ S.HCl
296140	cyclopropyl	H	t-Bu	HCl	C ₃₂ H ₄₆ N ₄ O ₇ S.HCl
296141	Me	Me	t-Bu	HCl	C ₃₁ H ₄₆ N ₄ O ₇ S.HCl
296142	H	Me	t-Bu	HCl	C ₃₀ H ₄₄ N ₄ O ₇ S.HCl

SOURCE – Pharmacia.

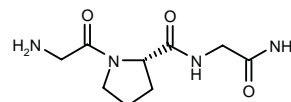
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1. Getman, D.P. et al. (Pharmacia Corp.) *Bis-amino acid hydroxyethylamino sulfonamide retroviral protease inhibitors*. EP 1076062, US 6143788, WO 9628464.

GPG-NH₂

296107

Glycyl-L-prolyl-glycinamide



C₉ H₁₆ N₄ O₃; Mol wt: 228.2504

ACTION – Anti-HIV agent, a tripeptide amide viral capsid protein polymerization inhibitor that prevents the formation of new functional virus particles and their release from infected cells. *In vitro*, compound is reported to be effective against all HIV strains including those resistant to available treatments, and the development of resistance has not been seen. In pigs, no side effects were observed after daily i.v. doses of 300 mg/kg for a month. A phase I clinical trial in healthy volunteers showed that GPG-NH₂ is well tolerated after administration of 2-8 g p.o. and 800 mg s.c. In a phase I/II clinical trial in treatment-naïve HIV-1-infected patients, compound was also proven to be effective and safe when given p.o. (12 g) for 14 days; reductions in viral load were seen at 10 days postdosing and persisted for a long time after treatment, apparently due to the slow uptake of compound and release from cells (half-life approx. 5 days).

SOURCE – Tripep.

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3. *Complete clinical studies*. Tripep Web Site 2000, Nov 21.
4. *New trials provide hope for HIV patients*. Tripep Press Release 2000, May 24.
5. *New unique drug against HIV available in two years*. Tripep Press Release 1999, Nov 15.

6. *Swedish HIV drug on the market in 2003.* Tripep Press Release 2000, June 19.

7. *The first patient has started its treatment in Tripep's phase II study of GPG.* Tripep Press Release 2000, Oct 27.

8. *Tripep carries out successful new share issue.* Tripep Press Release 2000, Feb 16.

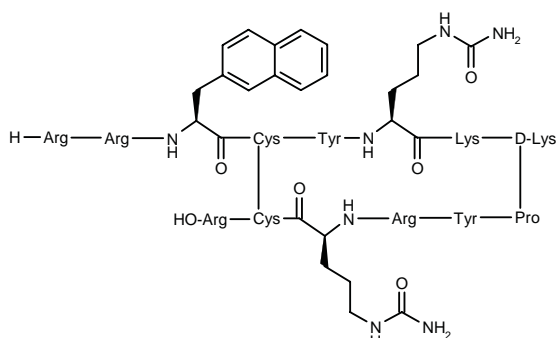
9. *Tripep is continuing the development of their new HIV-drug.* Tripep Press Release 2000, Sept 21.

10. Tripep Third Quarter Rep 2000, Oct 12.

TC-14003

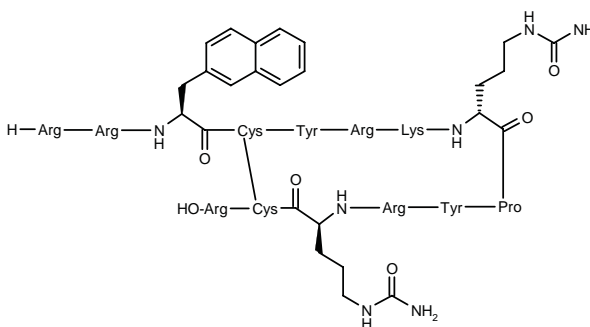
297807

L-Arginyl-L-arginyl-L-(2-naphthyl)alanyl-L-cysteinyl-L-tyrosyl-L-citrullinyl-L-lysyl-D-lysyl-L-prolyl-L-tyrosyl-L-arginyl-L-citrullinyl-L-cysteinyl-L-arginine cyclic (4-13)-disulfide



C90 H140 N32 O19 S2; Mol wt: 2038.4330

ACTION – Anti-HIV agent, an analogue of the specific inhibitor of chemokine CXCR4 receptors T-104. The compound has comparable anti-HIV activity to T-104 ($EC_{50} = 2.8$ nM vs. 3.3 nM) but lower cytotoxicity ($CC_{50} > 80$ μ M vs. >1 μ M). Another compound from this series is:



TC-14005 [297809]: C90 H140 N34 O19 S2

SOURCES – Kagoshima University, Kagoshima (JP); Kyoto University, Kyoto (JP); University of Louisville, Louisville, KY (US); Tokyo Medical Dental University, Tokyo (JP).

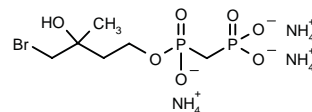
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TREATMENT OF PROTOZOAL DISEASES

295631

Methylenediphosphonic acid 4-bromo-3-hydroxy-3-methylbutyl monoester triammonium salt



C6 H12 Br O7 P2 . 3 H4 N; Mol wt: 392.1216

ACTION – A selective inhibitor of $T\gamma 9\delta 2$ (also known as $T\gamma 2\delta 2$) lymphocytes, potentially useful for the treatment of disorders involving activation of these lymphocytes, particularly parasitic diseases such as malaria, leishmaniasis and toxoplasmosis, autoimmune diseases such as Behçet's disease and multiple sclerosis, and bacterial infections such as brucellosis, salmonellosis and tuberculosis. *In vitro*, compound inhibited BrHPP-induced cytotoxicity of $T\gamma 9\delta 2$ lymphocytes with an IC_{50} value of 15 μ M, while no effects were observed against antigen-stimulated $T\gamma 8\delta 3$ lymphocytes; similar results were obtained using other inducing agents instead of BrHPP. A representative compound from a series of diphosphonate derivatives.

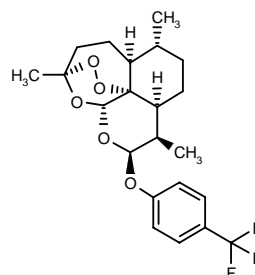
SOURCES – INSERM, Paris Cedex (FR); SangStat.

REFERENCES

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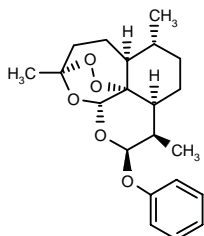
297912

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-Trimethyl-10-[4-(trifluoromethyl)phenoxy]decahydro-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin



C22 H27 F3 O5; Mol wt: 428.4443

ACTION – Antimalarial agent, a potent C-10-phenoxy derivative of dihydroartemisinin, with superior *in vitro* activity compared to artemisinin against *Plasmodium falciparum* (IC_{50} = 5.29 and 11.15 nM, respectively). In a mouse model of malaria, compound was active orally against *Plasmodium berghei* and s.c. against *Plasmodium yoelli*, with respective ED_{50} values of 2.7 and 2.2 mg/kg compared to respective ED_{50} values of 4.4 and 3.6 mg/kg for sodium artesunate. Preliminary metabolism studies indicated that compound is not metabolized to dihydroartemisinin and that it would therefore be expected to have a longer half-life and potentially lower neurotoxicity compared to first-generation compounds such as artemether and arteether. Another related compound is:



297913: C21 H28 O5

SOURCES – Johns Hopkins University, Baltimore, MD (US); University of Liverpool, Liverpool (GB); Ultrafine.

REFERENCES

- O'Neill, P.M. and Ward, S.A. (Ultrafine Ltd.) *Peroxide-based antimalarial cpds.* WO 0104123.
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- O'Neill, P.M. et al. *Synthesis, antimalarial activity, biomimetic iron(II) chemistry, and in vivo metabolism of novel, potent C-10-phenoxy derivatives of dihydroartemisinin.* J Med Chem 2001, 44(1): 58.

ARTEMOTIL⁺

Prop INN

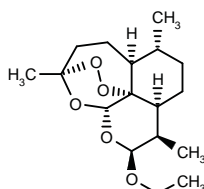
140796

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-10-Ethoxy-3,6,9-trimethyldecahydro-3,12-epoxy-12*H*-pyrano[4,3-*J*]-1,2-benzodioxepin

β-Dihydroqinghaosu ethyl ether

β-Dihydroartemisin ethyl ether

β-Arteether
SM-227



C17 H28 O5; Mol wt: 312.4032

ACTION – Blood schizontocide for *Plasmodium falciparum*, active against *P. falciparum* from the very early blood stages until the early gametocytes.

INDICATION – Treatment of severe *P. falciparum* malaria infections in children and adolescents 16 year old and under.

PRESENTATION – Ampoules of solution for i.m. injection, 50 mg/ml and 150 mg/ml.

PROPRIETARY NAME – Artecef (NL).

SOURCE – Artecef.

REFERENCES

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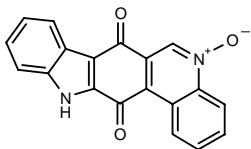
39. *Proposed international nonproprietary names (Prop. INN): List 80*. WHO Drug Inf 1998, 12(4): 253.

*See **Arteether** Drug Data Rep 1988, 010(06): 0503.

CALOTHRIXIN A

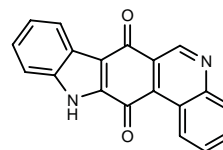
297512

12,13-Dihydro-7H-indolo[3,2-j]phenanthridine-7,13-dione 5-oxide



C19 H10 N2 O3; Mol wt: 314.2990

ACTION – Antimalarial and antineoplastic agent, a pentacyclic metabolite isolated from the cyanobacteria *Calothrix* shown to inhibit the growth of chloroquine-resistant *Plasmodium falciparum* with an IC_{50} value of 58 nM compared to 83 nM for chloroquine. Compound also showed cytotoxic activity against human cervical cancer HeLa cells (IC_{50} = 40 nM). Another related bioactive metabolite is:



Calothrixin B [297511]: C19 H10 N2 O2

SOURCE – Australian National University, Canberra (AU).

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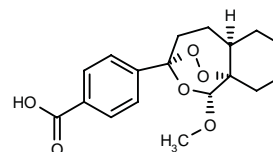
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MHP-34a

295527

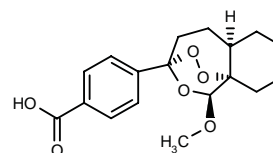
4-[(1S,6R,9(S),12R)-12-Methoxy-10,11,13-trioxatricyclo-[7.2.2.0^{1,6}]tridec-9-yl]benzoic acid

4-[(3R,5aS,9aR,10S)-10-Methoxyhexahydro-3,9a-(epoxymethano)-9aH-1,2-benzodioxepin-3(4H)-yl]benzoic acid



C18 H22 O6; Mol wt: 334.3658

ACTION – Water-soluble trioxane with antiparasitic properties, particularly useful for the treatment of malaria and cerebral toxoplasmic encephalitis. It showed high efficacy in mice infected with *Plasmodium berghei* following both oral (ED_{90} = 46 mg/kg/day x 4) and i.v. administration (ED_{90} = 60 mg/kg/day x 4). MHP-34a was nontoxic at therapeutic doses and caused no hemolysis of erythrocytes when administered i.v. to rats for 14 days. Another particularly preferred trioxane is:



MHP-34b [295529]: C18 H22 O6

SOURCE – Johns Hopkins University, Baltimore, MD (US).

REFERENCES

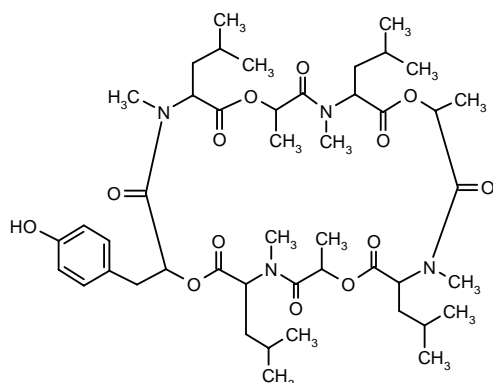
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TREATMENT OF HELMINTHIC DISEASES

PF-1022G

296437

2-(4-Hydroxybenzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,14,20,22-heptamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-3,6,9,12,15,18,21,24-octaone



C46 H72 N4 O13; Mol wt: 889.0898

ACTION – Cyclic depsipeptide isolated from a culture of the fungus PF-1022 (FERM BP-2671) that exhibits anthelmintic activity.

SOURCE – Meiji Seika.

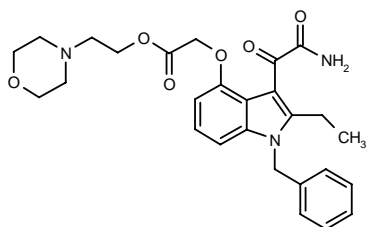
REFERENCES

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TREATMENT OF SHOCK

295946

2-[3-(2-Amino-2-oxoacetyl)-1-benzyl-2-ethyl-1*H*-indol-4-yloxy]acetic acid 2-(4-morpholinyl)ethyl ester



C27 H31 N3 O6; Mol wt: 493.5569

ACTION – Ester prodrug of the known human non-pancreatic secretory phospholipase A₂ (sPLA₂) inhibitor LY-315920⁺, with highly improved oral bioavailability compared to other esters of the parent compound, as demonstrated in pharmacokinetic studies in monkeys. Potentially useful for the treatment of septic shock.

SOURCE – Lilly.

REFERENCES

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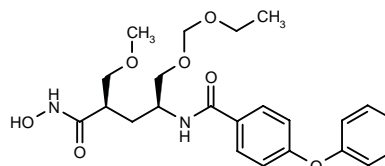
*Drug Data Rep 1997, 019(03): 0236.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

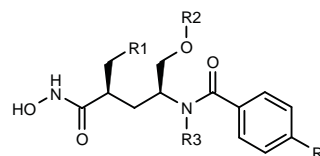
295616

(2*R*,4*S*)-5-(Ethoxymethoxy)-2-(methoxymethyl)-4-(4-phenoxybenzamido)pentanohydroxamic acid



C23 H30 N2 O7; Mol wt: 446.4970

ACTION – Matrix metalloproteinase inhibitor with IC₅₀ values of 0.0017 and 0.029 μM, respectively, against human gelatinase A and stromelysin. Potentially useful for the treatment and/or prevention of rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, interstitial nephritis, arteriosclerosis, pulmonary emphysema, hepatic cirrhosis, corneal injury, cancer, autoimmune diseases, angiogenesis, multiple sclerosis, aortic aneurysm, endometriosis, restenosis following PTCA, unstable angina, acute myocardial infarction and transient cerebral ischemic attacks. Other exemplified compounds from this series of 4-aminobutanoic acid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
295617	OMe	CH ₂ OEt	H	CN	C ₁₈ H ₂₆ N ₃ O ₆
295618	OMe	CH ₂ OEt	H	2-furyl	C ₂₁ H ₂₈ N ₂ O ₇
295619	CH ₂ CH ₂ Ph	H	Me	Br	C ₂₂ H ₂₇ BrN ₂ O ₄
295620	ethynyl-CH ₂ O	CH ₂ OEt	H	Cl	C ₁₉ H ₂₆ ClN ₂ O ₆
295621	ethynyl	H	Me	Br	C ₁₆ H ₁₈ BrN ₂ O ₄

SOURCE – Ono.

REFERENCES

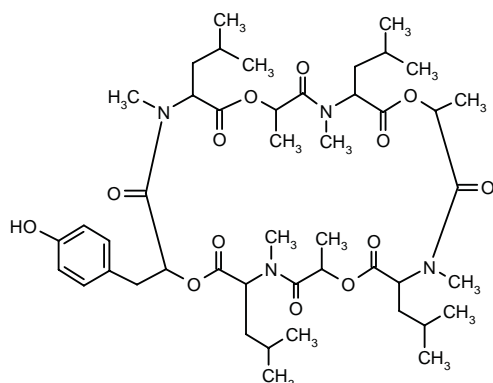
1. Takahashi, K. and Sugiura, T. (Ono Pharmaceutical Co., Ltd.) *4-Aminobutanoic acid derivs. and drugs containing these derivs. as the active ingredient*. WO 0059865.

TREATMENT OF HELMINTHIC DISEASES

PF-1022G

296437

2-(4-Hydroxybenzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,14,20,22-heptamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-3,6,9,12,15,18,21,24-octaone



C46 H72 N4 O13; Mol wt: 889.0898

ACTION – Cyclic depsipeptide isolated from a culture of the fungus PF-1022 (FERM BP-2671) that exhibits anthelmintic activity.

SOURCE – Meiji Seika.

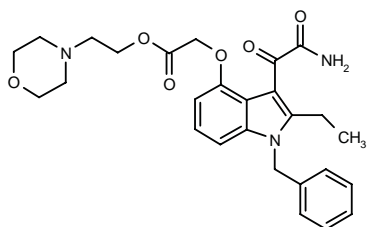
REFERENCES

1. Ohya, M. et al. (Meiji Seika Kaisha, Ltd.) *Cyclic depsipeptide PF 1022G*. US 6146853.

TREATMENT OF SHOCK

295946

2-[3-(2-Amino-2-oxoacetyl)-1-benzyl-2-ethyl-1*H*-indol-4-yloxy]acetic acid 2-(4-morpholinyl)ethyl ester



C27 H31 N3 O6; Mol wt: 493.5569

ACTION – Ester prodrug of the known human non-pancreatic secretory phospholipase A₂ (sPLA₂) inhibitor LY-315920⁺, with highly improved oral bioavailability compared to other esters of the parent compound, as demonstrated in pharmacokinetic studies in monkeys. Potentially useful for the treatment of septic shock.

SOURCE – Lilly.

REFERENCES

1. Sawyer, J.S. et al. (Eli Lilly and Company) *Morpholino-N-ethyl ester deriv. of an indole sPLA₂ inhibitor*. US 6140327, WO 0069818.

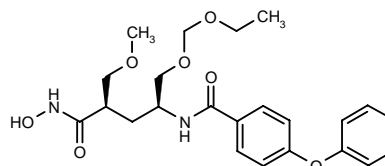
*Drug Data Rep 1997, 019(03): 0236.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

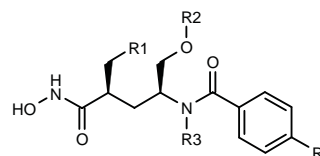
295616

(2*R*,4*S*)-5-(Ethoxymethoxy)-2-(methoxymethyl)-4-(4-phenoxybenzamido)pentanohydroxamic acid



C23 H30 N2 O7; Mol wt: 446.4970

ACTION – Matrix metalloproteinase inhibitor with IC₅₀ values of 0.0017 and 0.029 μM, respectively, against human gelatinase A and stromelysin. Potentially useful for the treatment and/or prevention of rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, interstitial nephritis, arteriosclerosis, pulmonary emphysema, hepatic cirrhosis, corneal injury, cancer, autoimmune diseases, angiogenesis, multiple sclerosis, aortic aneurysm, endometriosis, restenosis following PTCA, unstable angina, acute myocardial infarction and transient cerebral ischemic attacks. Other exemplified compounds from this series of 4-aminobutanoic acid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
295617	OMe	CH ₂ OEt	H	CN	C ₁₈ H ₂₆ N ₃ O ₆
295618	OMe	CH ₂ OEt	H	2-furyl	C ₂₁ H ₂₈ N ₂ O ₇
295619	CH ₂ CH ₂ Ph	H	Me	Br	C ₂₂ H ₂₇ BrN ₂ O ₄
295620	ethynyl-CH ₂ O	CH ₂ OEt	H	Cl	C ₁₉ H ₂₆ ClN ₂ O ₆
295621	ethynyl	H	Me	Br	C ₁₆ H ₁₈ BrN ₂ O ₄

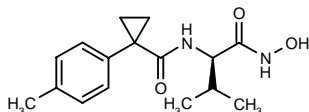
SOURCE – Ono.

REFERENCES

1. Takahashi, K. and Sugiura, T. (Ono Pharmaceutical Co., Ltd.) *4-Aminobutanoic acid derivs. and drugs containing these derivs. as the active ingredient*. WO 0059865.

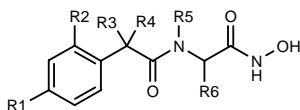
295622

3-Methyl-2(*R*)-[1-(4-methylphenyl)cyclopropylcarbox-amido]butyroxamic acid

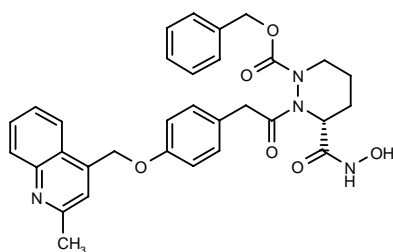


C16 H22 N2 O3; Mol wt: 290.3608

ACTION – Inhibitor of matrix metalloproteinases, TNF- α and aggrecanase that acts as an antiinflammatory agent and prevents cartilage degradation, and is thus potentially useful for the treatment of osteoarthritis and rheumatoid arthritis. Also claimed for the treatment of periodontitis, gingivitis, corneal ulceration, solid tumor growth, neo-vascular glaucoma, multiple sclerosis and psoriasis. Other specifically claimed amide derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
295623	OMe	H	-CH2CH2-	H	(R)-CH2-CH2SO2Me		C ₁₆ H ₂₂ N ₂ O ₆ S
295624	Cl	Cl	-CH2CH2-	Me	(R)-i-Pr		C ₁₆ H ₂₀ Cl ₂ N ₂ O ₃
295625	2,4-(Me)2-PhCH2O	H	-CH2CH2-	Me	(S)-Me		C ₂₃ H ₂₈ N ₂ O ₄
295626	3-Ph-5-isoxazolyl-CH2O	H	-CH2CH2-	Me	(S)-Me		C ₂₄ H ₂₅ N ₃ O ₅
295627	OCH2Ph	H	(S)-t-Bu-OCONH	H	Me	(S)-Me	C ₂₄ H ₃₁ N ₃ O ₆
295629	3,5-(Me)2-PhCH2O	H	Me	H	H	(R)-Me	C ₂₁ H ₂₆ N ₂ O ₄



295628: C32 H32 N4 O6

SOURCE – DuPont Pharmaceuticals.

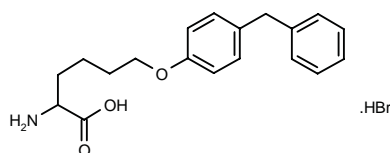
REFERENCES

1. Duan, J. (DuPont Pharmaceuticals Co.) *Novel amide derivs. as inhibitors of matrix metalloproteinases, TNF- α , and aggrecanase*. WO 0059874.

295630

6-(4-Benzylphenoxy)-DL-norleucine hydrobromide

2-Amino-6-(4-benzylphenoxy)hexanoic acid



C19 H23 N O3 . HBr; Mol wt: 394.3066

ACTION – Leukotriene LTA₄ hydrolase inhibitor with anti-inflammatory, antiarthritic and antipsoriatic activity.

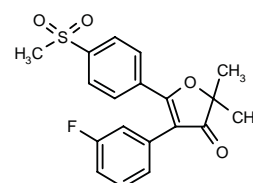
SOURCES – Bioprojet; INSERM, Paris Cedex (FR).

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1. Danvy, D. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]; Bioprojet) *LTA₄ hydrolase inhibitors*. FR 2791982, WO 0059864.

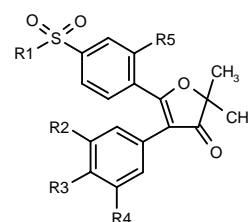
295837^{1,2}

4-(3-Fluorophenyl)-2,2-dimethyl-5-[4-(methylsulfonyl)phenyl]furan-3(2*H*)-one



C19 H17 F O4 S; Mol wt: 360.4033

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor with IC₅₀ values of 0.02 and 5 μ g/ml, respectively, against COX-2 and COX-1 in murine peritoneal macrophages. Compound exhibited good efficacy *in vivo*, as demonstrated in rat models of carrageenan-induced paw edema (36% inhibition at 3 mg/kg p.o. vs. 28% inhibition for indomethacin at 1 mg/kg p.o.), adjuvant-induced arthritis (ED₅₀ = 0.07 mg/kg p.o.) and carrageenan-induced thermal hyperalgesia (27% inhibition at 1 mg/kg p.o.), and in the murine acetic acid-induced writhing assay (ED₅₀ = 8.3 mg/kg p.o.), while it was shown to be devoid of ulcerogenic side effects in rats at 30 mg/kg p.o. A representative compound from a series of 4,5-diaryl-3(2*H*)-furanone derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
295838 ^{1,2}	Me	F	H	F	H	C ₁₉ H ₁₆ F ₂ O ₄ S
295839 ^{1,2}	Me	H	H	CF3	H	C ₂₀ H ₁₇ F ₃ O ₄ S
295840	NH2	H	H	Cl	H	C ₁₈ H ₁₆ ClNO ₄ S
295843	NH2	H	H	F	H	C ₁₈ H ₁₆ FNO ₄ S
295844	NH2	H	F	H	F	C ₁₈ H ₁₅ F ₂ NO ₄ S

SOURCE – Pacific Corp.

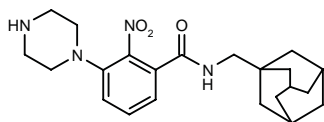
REFERENCES

1. Shin, S.S. et al. (Pacific Corp.) *4,5-Diaryl-3(2H)-furanone derivs. as cyclooxygenase-2 inhibitors*. WO 0061571.

2. Shin, S.S. et al. *2,2-Dimethyl-4,5-diaryl-3(2H)furanone derivatives as selective cyclooxygenase-2 inhibitors*. Bioorg Med Chem Lett 2001, 11(2): 165.

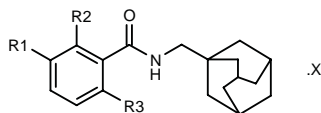
295886

N-(1-Adamantylmethyl)-2-nitro-3-(1-piperazinyl)benzamide



C₂₂ H₃₀ N₄ O₃; Mol wt: 398.5040

ACTION – Agent for the treatment or prevention of inflammatory, immune and cardiovascular diseases, particularly rheumatoid arthritis, asthma and chronic obstructive pulmonary disease (COPD), a P2X₇ receptor (previously known as P2Z receptor) antagonist. Other specifically claimed compounds from this series of adamantane derivatives include the following:



Compound	R1	R2	R3	R4	Formula
295887	1-Piz	Cl	H		C ₂₂ H ₃₀ ClN ₃ O
295888	3-pyrrolidinyl-O	H	Cl	HCl	C ₂₂ H ₂₉ ClN ₂ O ₂ ·HCl
295889	3-quinuclidinyl-NHCH ₂	H	Cl		C ₂₆ H ₃₆ ClN ₃ O
295890	cis-perhydro-pyrrolo[3,4-c]pyrrol-2-yl	H	Cl	HCl	C ₂₅ H ₃₄ ClN ₃ O·HCl
295891	3-Pip-CH(OH)	H	Cl	HCl	C ₂₄ H ₃₃ ClN ₂ O ₂ ·HCl
295892	4-Pip-CH ₂ CH ₂ O	H	Cl	HCl	C ₂₅ H ₃₅ ClN ₂ O ₂ ·HCl

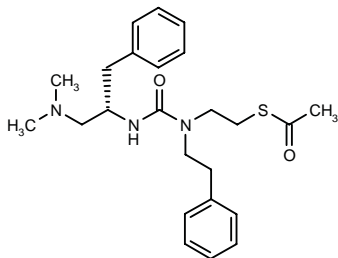
SOURCE – AstraZeneca.

REFERENCES

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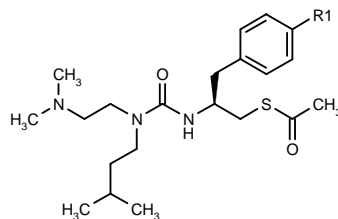
296055

N-[2-(Acetylsulfanyl)ethyl]-*N'*-[1(*S*)-benzyl-2-(dimethylamino)ethyl]-*N*-(2-phenylethyl)urea

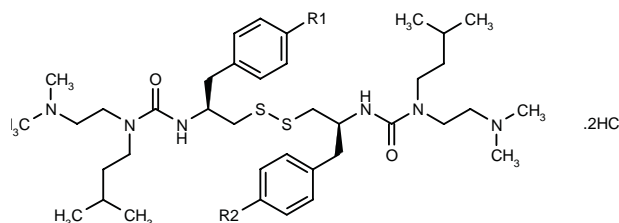


C₂₄ H₃₃ N₃ O₂ S; Mol wt: 427.6097

ACTION – TNF-α production inhibitor, potentially useful for the treatment of autoimmune diseases such as chronic rheumatoid arthritis, Crohn's disease and systemic lupus erythematosus, as well as cachexia, acute infections, allergy, fever, anemia and diabetes, among others. This compound inhibited lipopolysaccharide-stimulated TNF-α production by 83% in human monocytic THP-1 cells. Other exemplified *N*-substituted-*N'*-substituted urea derivatives include the following:



Compound	R1	Formula
296056	H	C ₂₁ H ₃₅ N ₃ O ₂ S
296057	Ph	C ₂₇ H ₃₉ N ₃ O ₂ S



Compound	R1=R2	Formula
296058	H	C ₃₈ H ₆₄ N ₆ O ₂ S ₂ ·2HCl
296059	Ph	C ₅₀ H ₇₂ N ₆ O ₂ S ₂ ·2HCl

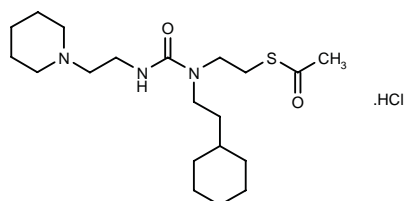
SOURCE – Santen.

REFERENCES

1. Mita, S. et al. (Santen Pharmaceutical Co., Ltd.) *N*-Subst.-*N'*-subst. urea deriv. and medicinal compns. containing the same. JP 2000351761, WO 0061548.

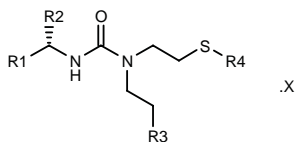
296060

N-[2-(Acetylsulfanyl)ethyl]-*N*-(2-cyclohexylethyl)-*N'*-[2-(1-piperidiny)ethyl]urea hydrochloride



C₂₀ H₃₇ N₃ O₂ S · HCl; Mol wt: 420.0582

ACTION – TNF-α production inhibitor, potentially useful for the treatment of autoimmune diseases such as chronic rheumatoid arthritis, Crohn's disease and systemic lupus erythematosus, as well as cachexia, acute infections, allergy, fever, anemia and diabetes, among others. This compound inhibited lipopolysaccharide-stimulated TNF-α production by 94% in human monocytic THP-1 cells. Other exemplified *N*-substituted-*N'*-substituted urea derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
296061	4-Me-1-Piz-CH2	CH2Ph	Ph	Ac		C ₂₇ H ₃₈ N ₄ O ₂ S
296062	1,2,3,6-tetrahydro-1-Pyr-CH2	H	cyclohexyl	Ac		C ₂₀ H ₃₅ N ₃ O ₂ S
296063	4-N(Me)2-1-Pip-CH2	H	cyclohexyl	Ac	2HCl	C ₂₂ H ₄₂ N ₄ O ₂ S.2HCl
296064	1-pyrrolidinyl-CH2	H	cyclohexyl	Ac		C ₁₉ H ₃₅ N ₃ O ₂ S
296065	1-pyrrolidinyl-CH2CH2	H	cyclohexyl	Ac		C ₂₀ H ₃₇ N ₃ O ₂ S
296066	1-Pip-CH2CH2	H	cyclohexyl	Ac		C ₂₁ H ₃₉ N ₃ O ₂ S
296067	hexahydro-1H-azepin-1-yl-CH2	H	cyclohexyl	Ac		C ₂₁ H ₃₉ N ₃ O ₂ S
296068	1-Et-2-pyrrolidinyl	H	cyclohexyl	Ac		C ₂₀ H ₃₇ N ₃ O ₂ S
296069	1-Me-4-Pip	H	cyclohexyl	Ac	HCl	C ₂₀ H ₃₇ N ₃ O ₂ S.HCl
296070	1-Pip-CH2	H	cyclohexyl	Me	HCl	C ₁₉ H ₃₇ N ₃ OS.HCl

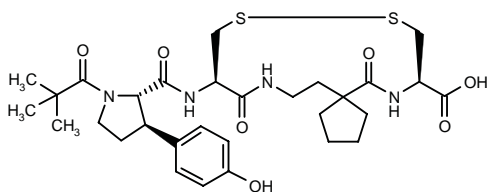
SOURCE – Santen.

REFERENCES

1. Mita, S. et al. (Santen Pharmaceutical Co., Ltd.) *N*-Subst.-*N'*-substd. urea deriv. and use thereof as TNF- α production inhibitor. JP 2000351764, WO 0061552.

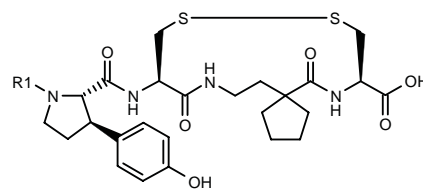
296366

13(*R*)-[1-(2,2-Dimethylpropionyl)-3(*R*)-(4-hydroxyphenyl)-pyrrolidin-2(*S*)-ylcarboxamido]-6,14-dioxo-10,11-dithia-7,15-diazaspiro[4.12]heptadecane-8(*R*)-carboxylic acid



C30 H42 N4 O7 S2; Mol wt: 634.8148

ACTION – Agent for the treatment of chronic inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma, pulmonary inflammation and inflammatory bowel disease that acts by inhibiting the binding of α_4 integrin-expressing cells to cell adhesion molecules of the endothelium, giving IC₅₀ values of 0.14 nM in an ELISA VLA-4/VCAM-1 assay and of 0.18 nM in a VLA-4/VCAM-1 Ramos cell-based assay. Other specifically claimed compounds from this series of pyrrolidinecarboxylamino cyclic disulfides are:



Compound	R1	Formula
296367	H	C ₂₅ H ₃₄ N ₄ O ₆ S ₂
296368	Ac	C ₂₇ H ₃₆ N ₄ O ₇ S ₂
296369	SO ₂ Me	C ₂₆ H ₃₆ N ₄ O ₈ S ₃

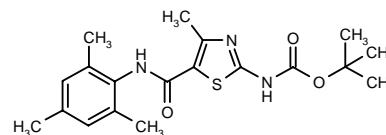
SOURCE – Roche.

REFERENCES

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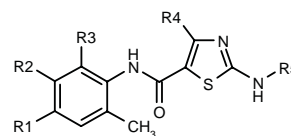
296370

N-[4-Methyl-5-[*N*-(2,4,6-trimethylphenyl)carbamoyl]-thiazol-2-yl]carbamic acid *tert*-butyl ester



C19 H25 N3 O3 S; Mol wt: 375.4905

ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, fyn, Lyn, Src, Yes, Hck, Fgr and Blk, as well as receptor tyrosine kinases such as HER1 and HER2, with potential in the treatment of a broad range of disorders including rheumatoid arthritis, multiple sclerosis, lupus, transplant rejection, graft-versus-host disease, inflammatory bowel disease, T-cell-mediated hypersensitivity disease, psoriasis, cancer, allergic diseases, asthma, ischemia–reperfusion injury and diabetic retinopathy. Other specifically claimed cyclic compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
296371	Me	H	Me	Me	2,5-(F)2-PhCO	C ₂₁ H ₁₉ F ₂ N ₃ O ₂ S
296372	Me	H	Me	Me	2-benzothienyl-CO	C ₂₃ H ₂₁ N ₃ O ₂ S ₂
296373	Me	H	Me	Me	CON(i-Pr)2	C ₂₁ H ₃₀ N ₄ O ₂ S
296374	Me	H	Me	Me	5-indolyl-NHCO	C ₂₃ H ₂₃ N ₅ O ₂ S
296375	H	-CH=CHCH=CH-	Me	Me	CONHBu	C ₂₁ H ₂₄ N ₄ O ₂ S
296376	H	H	Cl	H	COCH(Me)Pr	C ₁₇ H ₂₀ ClN ₃ O ₂ S
296377	H	H	Me	H	3-pyridazinyl	C ₁₆ H ₁₅ N ₅ OS
296378	H	H	Cl	H	6-[1-imidazolyl-(CH2)3]-2-Pyr	C ₂₂ H ₂₁ ClN ₆ OS
296379	H	H	Cl	H	6-[4-Me-1-Piz-(CH2)3NH]-2-Pyr	C ₂₄ H ₃₀ ClN ₇ OS
296380	H	H	Cl	H	1-[1-imidazolyl-(CH2)3]-4-benzimidazolyl	C ₂₄ H ₂₂ ClN ₇ OS

SOURCE – Bristol-Myers Squibb.

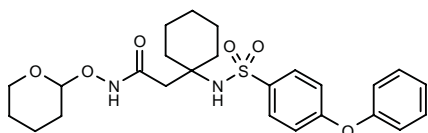
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296391

2-[1-(4-Phenoxyphenylsulfonamido)cyclohexyl]-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acetamide

2-[1-(4-Phenoxyphenylsulfonamido)cyclohexyl]-acetohydroxamic acid tetrahydropyranyl ester



C25 H32 N2 O6 S; Mol wt: 488.6018

ACTION – Inhibitor of matrix metalloproteinases (MMPs) and TNF- α with an IC_{50} of 4.7 nM when tested for inhibition of human MMP-13 (collagenase 3). Potentially useful for the treatment of arthritis, stroke, cancer, tissue ulceration, decubitus ulcer, restenosis, periodontal disease, epidermolysis bullosa, scleritis, psoriasis, AIDS, sepsis and septic shock, among others.

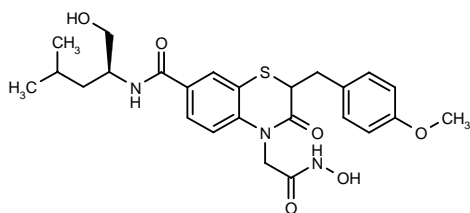
SOURCE – Fujisawa.

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296436

2-[7-[*N*-(1(*S*)-(Hydroxymethyl)-3-methylbutyl)carbamoyl]-2-(4-methoxybenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-4-yl]acetohydroxamic acid



C25 H31 N3 O6 S; Mol wt: 501.6009

ACTION – Matrix metalloproteinase (MMP) inhibitor with good activity against MMP-3 (stromelysin), MMP-13 (collagenase 3) and the like. It exhibited respective IC_{50} values of 0.053 and 0.0049 μ M when tested for MMP-3 and MMP-13 inhibition. Potentially useful in a wide range of diseases associated with excess or undesired MMP activity such as allergies, asthma, atherosclerosis, bronchitis, cancer, cardiac and cerebral disorders, Crohn's disease, osteoarthritis, osteopenia, etc.

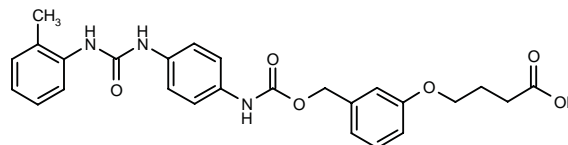
SOURCE – Sumitomo Pharmaceuticals.

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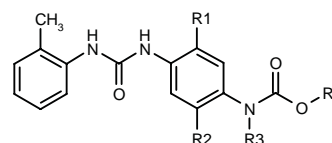
296469

4-[3-[*N*-(4-[3-(2-Methylphenyl)ureido]phenyl)carbamoyloxymethyl]phenoxy]butyric acid



C26 H27 N3 O6; Mol wt: 477.5143

ACTION – An inhibitor of the interaction of VCAM-1 and fibronectin with $\alpha_4\beta_1$ integrin, preferably useful for the treatment of multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease, psoriasis, atherosclerosis, transplant rejection, inflammatory bowel disease, insulin-dependent diabetes and glomerulonephritis. Other exemplified diphenylurea derivatives are:



Compound	R1	R2	R3	R4	Formula
296470	H	H	Me	3-[CO2H(CH2)3O]-PhCH2	C ₂₇ H ₂₉ N ₃ O ₆
296471	H	H	H	3-(CO2HCH2O)-PhCH2	C ₂₄ H ₂₃ N ₃ O ₆
296473	OMe	H	H	3-[CO2H(CH2)3O]-PhCH2	C ₂₇ H ₂₉ N ₃ O ₇
296475	H	H	H	3-(CO2HCH2O)-PhCH2CH2	C ₂₆ H ₂₅ N ₃ O ₆
296477	OMe	Me	H	4-[CO2H(CH2)3]-2-morpholinyl-CH2	C ₂₆ H ₃₄ N ₄ O ₇
296478	H	H	H	1-[CO2H(CH2)3]-3-Pip	C ₂₄ H ₃₀ N ₄ O ₅

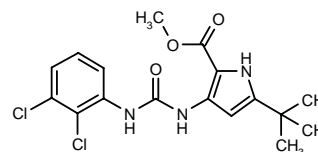
SOURCE – AstraZeneca.

REFERENCES

1. Oldham, K. (AstraZeneca AB) *Diphenylurea derivs*. WO 0064866.

298491

5-*tert*-Butyl-3-(2,3-dichlorophenylureido)-1*H*-pyrrole-2-carboxylic acid methyl ester



C17 H19 Cl2 N3 O3; Mol wt: 384.2611

ACTION – Highly potent p38 mitogen-activated protein (MAP) kinase inhibitor (IC_{50} = 6 nM against p38 α 2) reported to inhibit IL-6 production in human chondrosarcoma SW 1353 cells pretreated with IL-1 and TNF- α (IC_{50} = 79 nM). Potentially useful for the treatment of inflammatory diseases including arthritis and osteoporosis.

SOURCE – Bayer.

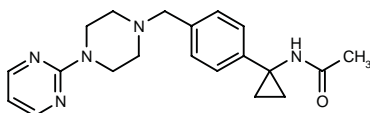
REFERENCES

1. Ranges, G. et al. (Bayer Corp.) *Inhibition of p38 kinase activity by aryl ureas*. WO 9852558.
2. Redman, A.M. et al. *p38 Kinase inhibitors for the treatment of arthritis and osteoporosis: Thienyl, furyl, and pyrrolyl ureas*. Bioorg Med Chem Lett 2001, 11(1): 9.

Y-39041*

290177

N-[1-[4-[4-(2-Pyrimidinyl)-1-piperazinylmethyl]phenyl]-cyclopropyl]acetamide



C₂₀ H₂₅ N₅ O; Mol wt: 351.4515

ACTION – Dual cytokine regulator proven to strongly attenuate lipopolysaccharide (LPS)-induced TNF- α production and simultaneously increase the production of IL-10 in mice following oral administration. Compound was also able to protect mice from LPS-induced death. In rats with established adjuvant-induced arthritis, daily doses of 3-30 mg/kg p.o. on days 15-20 significantly and dose-dependently reduced hind paw edema, with a longer lasting effect compared to prednisolone at 3 mg/kg p.o. In addition, both compound (3-30 mg/kg p.o.) and prednisolone (3 mg/kg p.o.) given to the arthritic rats prior to LPS on day 17 significantly reduced TNF- α and IL-6 production, but only Y-39041 induced an increase in LPS-stimulated IL-10 production. Potentially useful for the treatment of TNF- α -mediated chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease.

SOURCE – Welfide.

REFERENCES

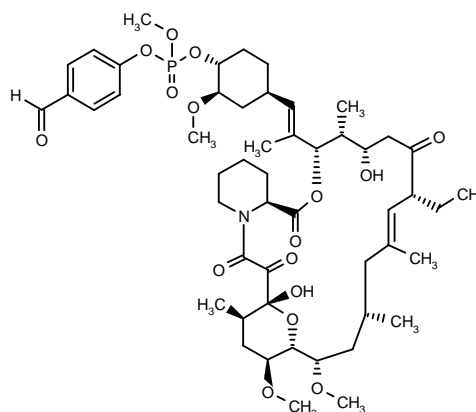
1. Adachi, K. et al. (Welfide Corporation) *Piperazine cpds. and medicinal use thereof*. EP 1029851, WO 9919301.
2. Fukuda, T. et al. *A novel dual regulator of tumor necrosis factor- α and interleukin-10 protects mice from endotoxin-induced shock*. Eur J Pharmacol 2000, 391(3): 317.
3. Hanano, T. et al. *Novel DMARDs on the basis of a new concept of dual cytokine regulation, TNF- α suppression and IL-10 augmentation*. Bioorg Med Chem Lett 2000, 10(9): 881.
4. Hisadome, M. et al. *A novel anti-rheumatic drug suppresses tumor necrosis factor- α and augments interleukin-10 in adjuvant arthritic rats*. Eur J Pharmacol 2000, 409(3): 331.

*Identified compound **290177** Drug Data Rep 2000, 022(09): 0827.

IMMUNOMODULATING AGENTS

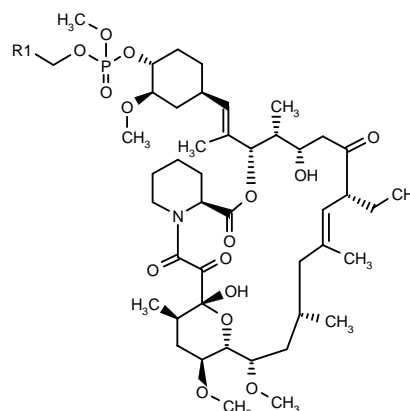
295405

(1*R*,9*S*,12*S*,13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*)-17-Ethyl-12-[(*E*)-2-[4(*R*)-[(4-formylphenoxy)(methoxy)phosphoryloxy]-3(*R*)-methoxycyclohex-1(*R*)-yl]-1-methylvinyl]-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetrone



C₅₁ H₇₆ N O₁₆ P; Mol wt: 990.1264

ACTION – Macrolide immunosuppressant whose activity was determined using the human mixed lymphocyte reaction (MLR; IC₅₀ = 0.75 nM). Compound was shown to be eliminated from the blood at 15 min postadministration to rats and is thus expected to exhibit reduced adverse systemic effects as compared to FK-506 (tacrolimus). Within this series of semisynthetic analogues of ascomycin and FK-506, the following are also included:



Compound	R1	Formula
295406	2-Pyr	C ₅₀ H ₇₇ N ₂ O ₁₅ P
295407	4-F-Ph	C ₅₁ H ₇₇ FNO ₁₅ P
295408	1-pyrrolidinyl-CH ₂	C ₅₀ H ₈₃ N ₂ O ₁₅ P

SOURCE – Abbott.

REFERENCES

1. Kawai, M. and Gunawardana, I.W. (Abbott Laboratories Inc.) *Phosphate containing macrocyclic immunomodulators*. WO 0058318.

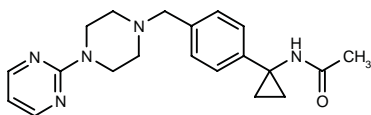
REFERENCES

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2. Redman, A.M. et al. *p38 Kinase inhibitors for the treatment of arthritis and osteoporosis: Thienyl, furyl, and pyrrolyl ureas*. Bioorg Med Chem Lett 2001, 11(1): 9.

Y-39041*

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SOURCE – Welfide.

REFERENCES

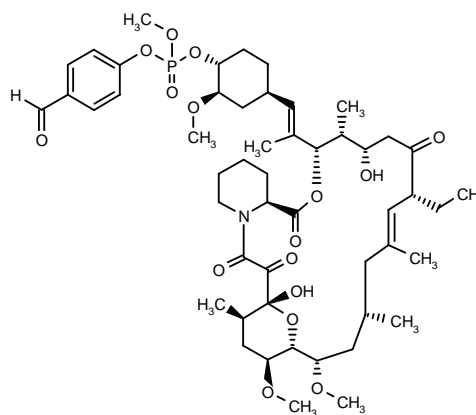
1. Adachi, K. et al. (Welfide Corporation) *Piperazine cpds. and medicinal use thereof*. EP 1029851, WO 9919301.
2. Fukuda, T. et al. *A novel dual regulator of tumor necrosis factor- α and interleukin-10 protects mice from endotoxin-induced shock*. Eur J Pharmacol 2000, 391(3): 317.
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4. Hisadome, M. et al. *A novel anti-rheumatic drug suppresses tumor necrosis factor- α and augments interleukin-10 in adjuvant arthritic rats*. Eur J Pharmacol 2000, 409(3): 331.

*Identified compound **290177** Drug Data Rep 2000, 022(09): 0827.

IMMUNOMODULATING AGENTS

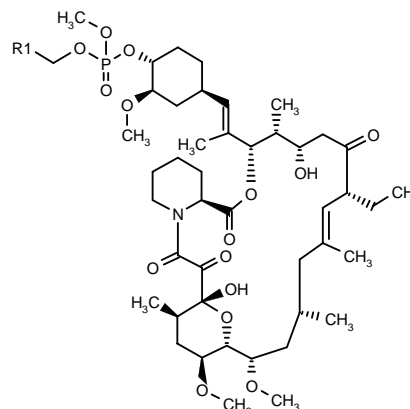
295405

(1*R*,9*S*,12*S*,13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*)-17-Ethyl-12-[(*E*)-2-[4(*R*)-[(4-formylphenoxy)(methoxy)phosphoryloxy]-3(*R*)-methoxycyclohex-1(*R*)-yl]-1-methylvinyl]-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetrone



C₅₁ H₇₆ N O₁₆ P; Mol wt: 990.1264

ACTION – Macrolide immunosuppressant whose activity was determined using the human mixed lymphocyte reaction (MLR; IC₅₀ = 0.75 nM). Compound was shown to be eliminated from the blood at 15 min postadministration to rats and is thus expected to exhibit reduced adverse systemic effects as compared to FK-506 (tacrolimus). Within this series of semisynthetic analogues of ascomycin and FK-506, the following are also included:



Compound	R1	Formula
295406	2-Pyr	C ₅₀ H ₇₇ N ₂ O ₁₅ P
295407	4-F-Ph	C ₅₁ H ₇₇ FNO ₁₅ P
295408	1-pyrrolidinyl-CH ₂	C ₅₀ H ₈₃ N ₂ O ₁₅ P

SOURCE – Abbott.

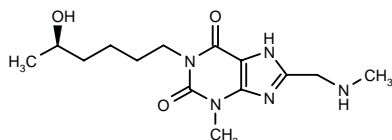
REFERENCES

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CT-12441

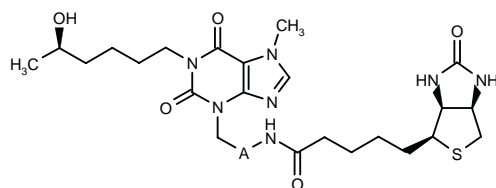
295794

1-[5(*R*)-Hydroxyhexyl]-3-methyl-8-(methylaminomethyl)-xanthine

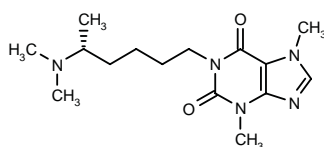


C14 H23 N5 O3; Mol wt: 309.3677

ACTION – An inhibitor of IL-12 intracellular signaling that is believed to act by inhibiting IL-12-dependent Th1 development. *In vitro*, compound inhibited IL-12-induced Th1 differentiation in anti-CD3-stimulated spleen T-cells with an IC₅₀ value of 19 μM. In addition, it was effective in an *in vivo* model of graft-versus-host disease in an irradiated F1 hybrid strain bred across a parental major H2 mismatch following oral administration. Potentially useful for the treatment of IL-12- or Th1-mediated disorders, particularly autoimmune, inflammatory and neurodegenerative disorders. Other compounds from this series of xanthine derivatives and analogues include the following:



Compound	A	Formula
CT-12460 [295797]	-(CH2)5-	C ₂₈ H ₄₅ N ₇ O ₅ S
CT-134410 [295802]	-CH2-	C ₂₄ H ₃₇ N ₇ O ₅ S



CT-11558 [295805]: C15 H25 N5 O2

SOURCE – Cell Therapeutics.

REFERENCES

1. Klein, J.P. et al. (Cell Therapeutics, Inc.) *Xanthine derivs. and analogs as cell signaling inhibitors*. WO 0061583.

HEXAVAC®

288618

Hexavalent vaccine that contains antigens from Haemophilus influenzae (Hib), hepatitis B, diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis virus

ACTION – Hexavalent pediatric vaccine.

INDICATION – Primary vaccination of infants 2 months and older against diphtheria, tetanus, pertussis (whooping cough), poliomyelitis, hepatitis B and invasive infections due to *H. influenzae* type b (Hib, bacterial meningitis).

PRESENTATION – Single-use prefilled syringe, 0.5 ml containing purified diphtheria toxoid ≥ 20 IU; purified tetanus toxoid ≥ 40 IU; purified pertussis toxoid 25 μg; purified pertussis filamentous hemagglutinin 25 μg; recombinant hepatitis B surface antigen 5.0 μg; inactivated poliomyelitis virus type 1 40 D units, type 2 8 D units and type 3 32 D units; *H. influenzae* polysaccharide type b 12 μg conjugated to tetanus toxoid (24 μg).

PROPRIETARY NAME – Hexavac (DE).

SOURCE – Aventis Pasteur.

REFERENCES

1. Caulfield, M.J. et al. *Immunogenicity of a hexavalent combination vaccine in rhesus monkeys*. Vaccine 2001, 19(7-8): 902.
2. *Aventis Pasteur launches Hexavac, a significant advance in childhood vaccination*. DailyDrugNews.com (Daily Essentials) 2001, Jan 19.
3. *Aventis updates 2000 achievements and highlights emerging pipeline products*. DailyDrugNews.com (Daily Essentials) 2001, March 20.
4. *Aventis updates R&D activities —pipeline "full and delivering"*. DailyDrugNews.com (Daily Essentials) 2000, May 23.
5. *Three new additions to the Aventis pipeline*. DailyDrugNews.com (Daily Essentials) 2000, March 24.

MENJUGATE®

280394

Meningococcal C capsular oligosaccharides conjugated to CRM197 (cross-reacting materials 197)

ACTION – Meningococcal group C conjugate vaccine.

INDICATION – Active immunization of children 12 months of age and older, adolescents and adults for the prevention of invasive disease caused by *Neisseria meningitidis* serogroup C.

PRESENTATION – Vials for i.m. injection; a single dose of 0.5 ml suspension contains 10 μg of the meningococcal group C oligosaccharide conjugated with 12.5-25.0 μg diphtheria CRM197 protein.

PROPRIETARY NAME – Menjugate (EI, GB).

SOURCES – Chiron; copromoted by Aventis Pasteur.

REFERENCES

1. MacDonald, N.E. et al. *Induction of immunologic memory by conjugates vs plain meningococcal C polysaccharide vaccine in toddlers*. JAMA - J Am Med Assoc 1998, 280: 1685.
2. MacLennan, J.M. et al. *Safety, immunogenicity, and induction of immunologic memory by a serogroup C meningococcal conjugate vaccine in infants*. JAMA - J Am Med Assoc 2000, 283(21): 2795.
3. *Chiron and Aventis Pasteur team up to promote and market vaccines*. DailyDrugNews.com (Daily Essentials) 2000, July 17.
4. *Chiron seeks U.K. approval for meningitis vaccine*. DailyDrugNews.com (Daily Essentials) 1999, Sept 14.
5. *Chiron to supply meningitis C vaccine to U.K.'s NHS*. DailyDrugNews.com (Daily Essentials) 1999, Oct 14.
6. *Chiron's Menjugate approved in Ireland*. DailyDrugNews.com (Daily Essentials) 2000, Aug 10.
7. *Meningococcal C meningitis vaccine approved for very young infants*. DailyDrugNews.com (Daily Essentials) 2000, Oct 19.
8. *Progress reported by Chiron in product pipeline during 2000*. DailyDrugNews.com (Daily Essentials) 2001, Feb 15.
9. *U.K.'s MCA approves another new meningitis C vaccine*. DailyDrugNews.com (Daily Essentials) 2000, March 2.

NEISVAC-C®**255582**

Group C meningococcal polysaccharide (GCMP)–tetanus toxoid (TT) conjugate vaccine

GCMP-TT

ACTION – Meningococcal group C polysaccharide conjugate vaccine.

INDICATION – Acute immunization of individuals 1 year of age and older for the prevention of invasive disease caused by *Neisseria meningitidis* serogroup C.

PRESENTATION – Single-dose syringe filled with 0.5 ml of suspension containing 10 µg meningococcal group C polysaccharide conjugated with 10-20 µg tetanus toxin protein adsorbed to 0.5 mg of aluminium hydroxide as adjuvant.

PROPRIETARY NAME – *NeisVac-C* (GB).

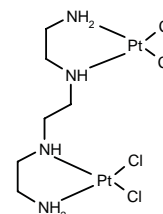
SOURCE – Baxter.

REFERENCES

1. Richmond, P. et al. *Phase I evaluation of a meningococcal C-tetanus toxoid conjugate vaccine*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst G-111.
2. Richmond, P.C. et al. *Meningococcal C conjugate vaccines are immunogenic and prime for memory after a single dose in toddlers*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst G252.
3. *Baxter achieves significant R&D milestones during 2000*. DailyDrugNews.com (Daily Essentials) 2001, Jan 31.
4. *Clinical trial shows promising results in development of new meningitis vaccine*. North American Vaccine, Inc. Press Release 1997, Feb 4.
5. *NeisVac-C meningococcal vaccine approved in U.K.* DailyDrugNews.com (Daily Essentials) 2000, July 21.
6. *North American Vaccine awarded contract to supply NeisVac-C in U.K.* DailyDrugNews.com (Daily Essentials) 1999, Oct 20.
7. *North American vaccine receives authorization to begin a phase II clinical trial of its investigational meningitis vaccine*. North American Vaccine, Inc. Press Release 1997, May 20.
8. *North American Vaccine submits NeisVac-C for U.K. approval*. DailyDrugNews.com (Daily Essentials) 2000, Jan 25.
9. *North American Vaccine to seek NeisVac-C approval in U.K. shortly*. DailyDrugNews.com (Daily Essentials) 2000, Jan 20.
10. *North American Vaccine updates development pipeline at H&Q*. DailyDrugNews.com (Daily Essentials) 1999, Jan 15.

ONCOLYTIC DRUGS**DNA-DAMAGING DRUGS****296219**

[µ-[*N,N'*-Bis[2-(amino-κ*N*)ethyl]-1,2-ethanediamine-κ*N*:κ*N'*]]tetrachlorodiplatinum

C₆ H₁₈ N₄ . 2 Cl₂ Pt; Mol wt: 678.2082

ACTION – A representative compound from a series of dinuclear platinum complexes, particularly cisplatin and carboplatin analogues, with potential for the treatment of cancer and AIDS. *In vitro*, compound exhibited comparable cytotoxicity to carboplatin against human hepatoma Hep 3B and human colon carcinoma Caco-2 cells, with IC₅₀ values of 18 and 6.2 µM, respectively, versus IC₅₀ values of 5 and 3.8 µM, respectively, for carboplatin.

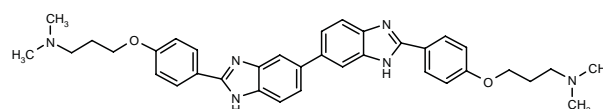
SOURCE – Unitech Pharmaceuticals.

REFERENCES

1. Shaw, J. (Unitech Pharmaceuticals, Inc.) *Platinum complexes for the treatment of cancer*. WO 0063219.
2. Shaw, J. (Unitech Pharmaceuticals, Inc.) *Dinuclear platinum complexes as cisplatin analogs for cancer treatment*. US 6130245.

NSC-D699127**296498**

5,5'-Bis[2-[4-[3-(dimethylaminopropoxy)phenyl]-1*H*-benzimidazole]

C₃₆ H₄₀ N₆ O₂; Mol wt: 588.7520

NEISVAC-C®**255582**

Group C meningococcal polysaccharide (GCMP)–tetanus toxoid (TT) conjugate vaccine

GCMP-TT

ACTION – Meningococcal group C polysaccharide conjugate vaccine.

INDICATION – Acute immunization of individuals 1 year of age and older for the prevention of invasive disease caused by *Neisseria meningitidis* serogroup C.

PRESENTATION – Single-dose syringe filled with 0.5 ml of suspension containing 10 µg meningococcal group C polysaccharide conjugated with 10-20 µg tetanus toxin protein adsorbed to 0.5 mg of aluminium hydroxide as adjuvant.

PROPRIETARY NAME – *NeisVac-C* (GB).

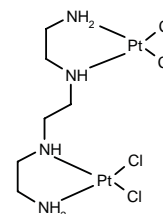
SOURCE – Baxter.

REFERENCES

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2. Richmond, P.C. et al. *Meningococcal C conjugate vaccines are immunogenic and prime for memory after a single dose in toddlers*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst G252.
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6. *North American Vaccine awarded contract to supply NeisVac-C in U.K.* DailyDrugNews.com (Daily Essentials) 1999, Oct 20.
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ONCOLYTIC DRUGS**DNA-DAMAGING DRUGS****296219**

[µ-[*N,N'*-Bis[2-(amino-κ*N*)ethyl]-1,2-ethanediamine-κ*N*:κ*N'*]]tetrachlorodiplatinum



C6 H18 N4 . 2 Cl2 Pt; Mol wt: 678.2082

ACTION – A representative compound from a series of dinuclear platinum complexes, particularly cisplatin and carboplatin analogues, with potential for the treatment of cancer and AIDS. *In vitro*, compound exhibited comparable cytotoxicity to carboplatin against human hepatoma Hep 3B and human colon carcinoma Caco-2 cells, with IC₅₀ values of 18 and 6.2 µM, respectively, versus IC₅₀ values of 5 and 3.8 µM, respectively, for carboplatin.

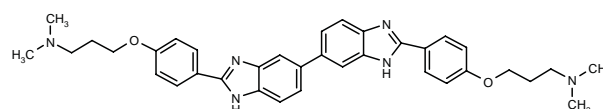
SOURCE – Unitech Pharmaceuticals.

REFERENCES

1. Shaw, J. (Unitech Pharmaceuticals, Inc.) *Platinum complexes for the treatment of cancer*. WO 0063219.
2. Shaw, J. (Unitech Pharmaceuticals, Inc.) *Dinuclear platinum complexes as cisplatin analogs for cancer treatment*. US 6130245.

NSC-D699127**296498**

5,5'-Bis[2-[4-[3-(dimethylaminopropoxy)phenyl]-1*H*-benzimidazole]



C36 H40 N6 O2; Mol wt: 588.7520

ACTION – Antineoplastic agent with potent growth inhibition activity against a panel of 60 human cancer cell lines (mean IC_{50} = 0.21 μ M) and against a small panel of ovarian cancer cell lines (mean IC_{50} = 0.31 μ M). Compound was also active against two cell lines possessing resistance to cisplatin and against P-glycoprotein-expressing doxorubicin-resistant ovarian cancer cell lines. Compound was found to bind to the A/T-rich minor groove of B-form DNA and to inhibit transcription. *In vivo*, compound given as single or multiple i.p. doses of 4-4.5 mg/kg showed antitumor activity in the hollow fiber assay with i.p.-implanted fibers containing human ovarian carcinoma CH1 or OVCAR-3. Antitumor activity was also seen in mice with established s.c.-implanted CH1 xenografts treated with multiple doses of 4 mg/kg i.p.

SOURCES – Institute of Cancer Research, London (GB); Queen's University of Belfast, Belfast (GB); University of Reading, Reading (GB).

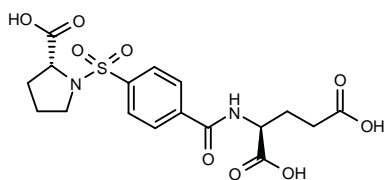
REFERENCES

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3. Neidle, S. et al. *Symmetric bis-benzimidazoles: New sequence selective DNA-binding molecules*. Chem Commun (London) 1999, 10: 929.

ANTIMETABOLITES

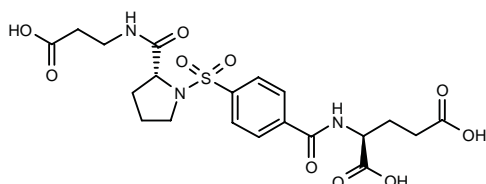
296077

2(S)-[4-[2(R)-Carboxypyrrolidin-1-ylsulfonyl]benzamido]-glutaric acid



C17 H20 N2 O9 S; Mol wt: 428.4160

ACTION – Thymidylate synthase inhibitor, potentially useful as an antitumor, antiparasitic, antibacterial, antifungal and antiviral agent. It demonstrated the ability to inhibit thymidylate synthase in an enzymatic assay and was reported to be competitive with respect to uridine 5'-monophosphate. Another exemplified tosylproline analogue is:



296078: C20 H25 N3 O10 S

SOURCE – Sunesis.

REFERENCES

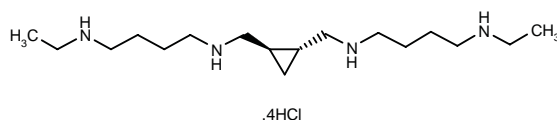
1. Erlanson, D.A. (Sunesis Pharmaceuticals, Inc.) *Tosylproline analogs as thymidylate synthase inhibitors*. US 6143776.

SL-11093

297412

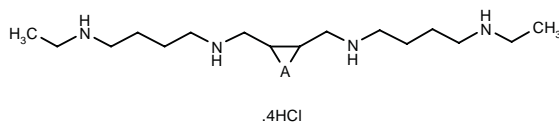
trans-N¹-Ethyl-N⁴-[2-[4-(ethylamino)butylaminomethyl]-cyclopropylmethyl]-1,4-butanediamine tetrahydrochloride

trans-1,2-Bis[4-(ethylamino)butylaminomethyl]cyclopropane tetrahydrochloride



C17 H38 N4 . 4HCl; Mol wt: 444.3588

ACTION – Polyamine analogue derived from BE-4-4-4, with improved cytotoxicity against human prostate cancer cell lines including DuPro, DU 145, LNCaP and PC-3 cells (IC_{50} = 0.059, 0.016, 0.21 and 1.6 μ M, respectively). Compound entered the cells and reduced cellular putrescine and spermidine pools, while exerting only a small effect on the spermine pool. This effect on polyamine pools was not correlated with its cytotoxicity, which appeared to be correlated with its specific molecular structure. Finally, compound exhibited significantly better systemic tolerability than BE-4-4-4. Within this series of conformationally restricted analogues of N¹,N¹⁴-bisethylhomospermine (BE-4-4-4), the following are also described:



Compound	A	Isomer	Formula
SL-11098 [297413]	-CH2-	cis	C ₁₇ H ₃₈ N ₄ .4HCl
SL-11099 [297414]	-(CH2)2-	trans	C ₁₈ H ₄₀ N ₄ .4HCl

SOURCE – SLIL Biomedical.

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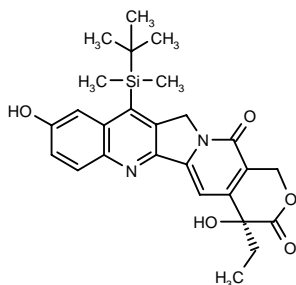
DNA-INTERCALATING DRUGS

DB-67*,1-12,14-23

274543

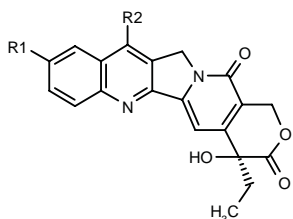
11-(*tert*-Butyldimethylsilyl)-4(*S*)-ethyl-4,9-dihydroxy-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14-dione

(20*S*)-7-(*tert*-Butyldimethylsilyl)-10-hydroxycamptothecin



C₂₆ H₃₀ N₂ O₅ Si; Mol wt: 478.6180

ACTION – Antineoplastic agent, a potent 7-silylcampothecin (silatecan) topoisomerase I inhibitor selected for further evaluation on the basis of its superior lipophilicity and stability in human blood and in the presence of human serum albumin compared to other camptothecins. Compound is 25 times more lipophilic than camptothecin and rapidly incorporates into cellular and liposomal bilayers. It is highly active in DNA cleavage assays, forms more stable topoisomerase I cleavage complexes than camptothecin and showed cytotoxic activity comparable to camptothecin against a variety of human tumor cell lines derived from several different tumor types in the NCI cytotoxicity screen (mean GI₅₀ = 21 nM). In particular, compound was significantly more active than camptothecin or analogues against human mammary carcinoma MDA-MB-435 cells (IC₅₀ = 100 nM). *In vivo*, it was well tolerated in mice when administered as repeated i.v. doses of 10 mg/kg, and it exerted comparable activity to topotecan in SCID mice bearing colon adenocarcinoma HC1 or glioma U-87. Further *in vivo* studies are in progress. Other specifically claimed compounds within this series of highly lipophilic silatecans are:



Compound	R1	R2	Formula
DB-174 [282913]	OH	CH ₂ CH ₂ Si(Me) ₃	C ₂₅ H ₂₈ N ₂ O ₅ Si
DB-202 [295449]	H	<i>t</i> -BuSi(Me) ₂	C ₂₆ H ₃₀ N ₂ O ₄ Si
DB-148 [296220]	H	Si(Me) ₂ (CH ₂) ₃ Cl	C ₂₅ H ₂₇ ClN ₂ O ₄ Si
DB-158 [296221]	OH	Si(Me) ₂ (CH ₂) ₃ Cl	C ₂₅ H ₂₇ ClN ₂ O ₅ Si

SOURCES – National Cancer Institute, Bethesda, MD (US); University of Pittsburgh, Pittsburgh, PA (US); Tigen Pharmaceuticals.

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- Isamo, T. et al. *Dual substitution at the 7- and 10- positions optimize 7-silyl-camptothecin (Silatecan) human plasma and blood stabilities*. Proc Amer Assoc Cancer Res 2001, 42: Abst 543.
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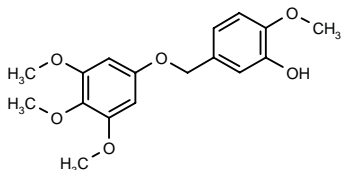
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ANTIMITOTIC DRUGS

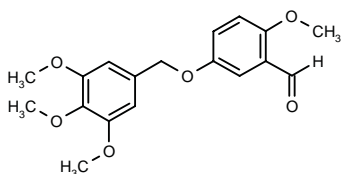
298502

2-Methoxy-5-(3,4,5-trimethoxyphenoxy)methyl)phenol



C17 H20 O6; Mol wt: 320.3390

ACTION – Antimitotic agent, a combretastatin A-4-like ether proven to inhibit the growth of human chronic myelogenous leukemia K-562 cells ($IC_{50} = 0.02 \mu M$), causing significant G2/M cell cycle arrest. Compound was also found to inhibit tubulin polymerization ($IC_{50} = 6.6 \mu M$) and to bind to the colchicine binding site ($IC_{50} = 36 \mu M$). *In vivo* studies to assess the antineoplastic activity of compound are in progress. Another related compound is:



298503: C18 H20 O6

SOURCES – Paterson Institute for Cancer Research, Manchester (GB); University of Science and Technology, Manchester (GB).

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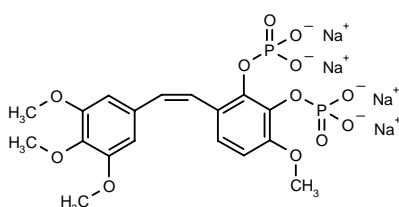
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COMBRETASTATIN A-1 PHOSPHATE

295643

3-Methoxy-6-[(Z)-2-(3,4,5-trimethoxyphenyl)vinyl]-1,2-benzenediol bis(dihydrogen phosphate) tetrasodium salt

CA1P



C18 H18 Na4 O12 P2; Mol wt: 580.2362

M.p. 168-70 °C.

ACTION – Sodium phosphate prodrug of combretastatin A-1 with excellent water solubility (120 mg/ml) and significantly improved antitumor activity compared to the parent drug. Compound inhibited the growth of murine lymphocytic leukemia P388 *in vitro* with an ED_{50} of $< 0.01 \mu g/ml$, and of several human cancer cell lines including pancreatic adenocarcinoma BxPC-3, ovarian carcinoma OVCAR-3, CNS cancer SF-295, non-small cell lung carcinoma NCI-H460, colon carcinoma KM2012 and prostate carcinoma DU 145 cells ($GI_{50} = 1.5, 0.024, 0.036, 0.038, 0.53$ and $0.034 \mu g/ml$, respectively). Selected for further studies.

SOURCES – Arizona State University, Tempe, AZ (US); Oxigene.

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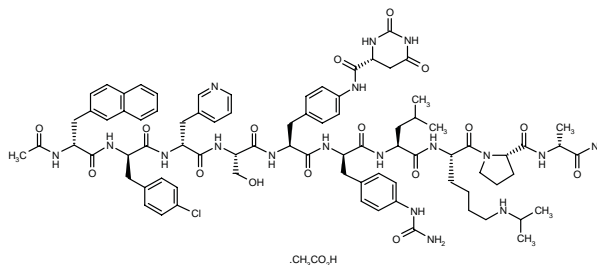
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HORMONAL AGENTS

FE-200486

274806

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-4-[2,6-dioxohexahydro-pyrimidin-4(*S*)-ylcarboxamido]-L-phenylalanyl-4-ureido-D-phenylalanyl-L-leucyl-*N*⁶-isopropyl-L-lysyl-L-prolyl-D-alaninamide



C82 H103 Cl N18 O16 . C2 H4 O2; Mol wt: 1692.3300

ACTION – Long-acting, water-soluble gonadotropin-releasing hormone receptor (GnRH) antagonist proven to behave as a highly selective, potent and competitive antagonist, as demonstrated in binding and functional assays ($K_i = 0.6 \text{ nM}$; $IC_{50} = 3 \text{ nM}$; $pA_2 = 8.9$), with low histamine-releasing potency compared to other GnRH antagonists. *In vivo*, compound given s.c. suppressed luteinizing hormone (LH) in castrated rats ($ED_{70} = 3 \mu g/kg$) and testosterone in intact rats ($ED_{70} = 1 \mu g/kg$), with a very long duration of action ($> 80\%$ inhibition of LH release at 96 h). After a dose of 2 mg/kg s.c., it completely inhibited LH levels for at least 40 days in castrated male rats and ovariectomized rhesus monkeys, LH returning to normal

levels at day 75 (rats) or 86 (monkeys); in intact rats, compound suppressed testosterone to castration levels and led to shrinkage of sex steroid-dependent organs. In rats with Dunning R-3327H prostatic adenocarcinoma, FE-200486 given at 2 mg/kg s.c. once a month completely suppressed testosterone levels and tumor growth, with an efficacy comparable to surgical castration. Potentially useful in the therapy of sex steroid-dependent pathologies and prostate cancer.

SOURCE – Ferring.

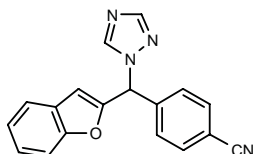
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MEN-11066*

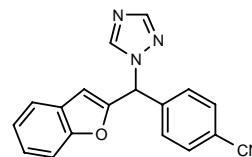
265119

(±)-4-[1-(Benzofuran-2-yl)-1-(1,2,4-triazol-1-yl)methyl]-benzonitrile



C₁₈ H₁₂ N₄ O; Mol wt: 300.3198

ACTION – Potent and selective aromatase inhibitor with a K_i value of 0.098 nM against human placental microsomal enzyme and greater potency than the reference compound anastrozole (K_i = 1.12 nM). In two human breast carcinoma MCF-7 sublines, MCF-7(TA) (with intrinsic aromatase activity) and MCF-7(hPA) (transfected with human placental aromatase cDNA), compound was more effective than anastrozole in inhibiting testosterone-induced proliferation (IC_{50} = 0.05 and 0.45 nM, respectively, for title compound vs. 1.2 and 7 nM, respectively, for anastrozole). MEN-11066 also inhibited androstenedione-stimulated proliferation of MCF-7(hPA) cells (IC_{50} = 0.15 nM vs. 9 nM for anastrozole), but did not inhibit the growth of estradiol-stimulated cells, demonstrating its specificity for aromatase. Potentially useful for the treatment of tumors that are highly responsive to estrogen such as breast cancer. Its enantiomers are:



Compound	Isomer	Formula
MEN-11623 [298806]	+	C ₁₈ H ₁₂ N ₄ O
MEN-11622 [298807]	-	C ₁₈ H ₁₂ N ₄ O

SOURCE – Menarini.

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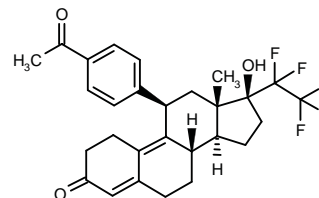
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2. Palma, C. et al. *Effect of the aromatase inhibitor, MEN 11066, on growth of two different MCF-7 sublines*. Eur J Pharmacol 2000, 409(2): 93.

*Identified compound **265119** Drug Data Rep 1998, 020(10): 0888.

ZK-230211

297093

11β-(4-Acetylphenyl)-17β-hydroxy-17-(pentafluoroethyl)-estra-4,9-dien-3-one



C₂₈ H₂₉ F₅ O₃; Mol wt: 508.5241

ACTION – Highly selective and potent progesterone receptor (PR) antagonist with reduced endocrine side effects. *In vitro*, compound proved to be a pure and potent antagonist at both PR isoforms (PR-A and PR-B; IC_{50} = 0.002 nM or less), a partial androgen agonist, exhibiting mainly antiandrogenic activity, and a weak glucocorticoid antagonist, with no effect at estrogen receptors. *In vivo*, it displayed contraceptive and antitumor activities. In juvenile estradiol/progesterone-stimulated rabbits, it was more potent than RU-486 in antagonizing progesterone-induced endometrial gland differentiation (ED_{50} = 6.3 mg/kg p.o.), while being devoid of intrinsic progestagenic activity, and it produced a complete abortifacient effect in pregnant rats at doses of 0.1 and 0.3 mg/day s.c., being 10 times more potent than RU-486. ZK-230211 inhibited the growth of DMBA-induced mammary tumors in rats, 50% of animals showing complete tumor regression at doses of 2 mg/kg s.c. or more. Potentially useful in estrogen replacement therapy and the treatment of breast cancer.

SOURCES – Jenapharm; Schering AG.

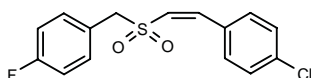
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

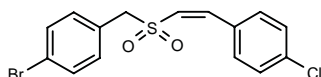
295330

(Z)-2-(4-Chlorophenyl)vinyl 4-fluorobenzyl sulfone



C15 H12 Cl F O2 S; Mol wt: 310.7748

ACTION – Antineoplastic agent proven to produce > 75% cell death when tested against breast cancer MCF-7, BT-20 and MDA-MB-435, prostate cancer LnCaP and DU 145, ovarian cancer OVCAR and SK-OV-3, lung cancer N417 and H157, renal cancer Caki-1 and Caki-2, and glioma U-87 and SW 1088 cell lines at a concentration of 2.5 mM, while exhibiting no cytotoxicity against normal murine fibroblast NIH3T3 and human fibroblast HFL cells. Compound is believed to act by interfering with the mitogen-activated protein kinase (MAPK) signal transduction pathway, in particular by modulating ERK and JNK kinases. Another specifically claimed compound from this series of (Z)-styryl sulfone derivatives is:



295331: C15 H12 Br Cl O2 S

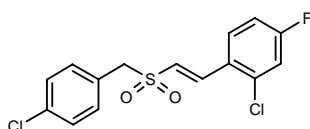
SOURCE – Temple University, Philadelphia, PA (US).

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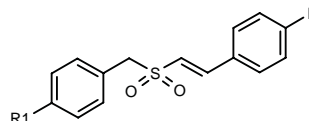
295474

4-Chlorobenzyl (E)-2-(2-chloro-4-fluorophenyl)vinyl sulfone



C15 H11 Cl2 F O2 S; Mol wt: 345.2199

ACTION – Antineoplastic agent that acts by interfering with the p38 mitogen-activated protein kinase (MAPK) signal transduction pathway, in particular by modulating ERK and JNK kinases. Compound produced > 80% cell death when tested against breast cancer MCF-7, prostate cancer DU 145, colorectal carcinoma DLD-1 and non-small cell lung cancer H157 cell lines at a concentration of 2.5 mM, while exhibiting no cytotoxicity against normal murine fibroblast NIH3T3 and human fibroblast HFL cells. Other compounds from this series of (E)-styryl sulfone derivatives include the following:



Compound	R1	Formula
295475	I	C ₁₅ H ₁₂ FIO ₂ S
295476	OMe	C ₁₆ H ₁₅ FO ₃ S

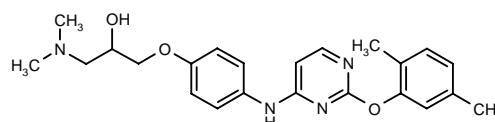
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295530

1-(Dimethylamino)-3-[4-[2-(2,5-dimethylphenoxy)pyrimidin-4-ylamino]phenoxy]propan-2-ol



C23 H28 N4 O3; Mol wt: 408.4992

ACTION – Cell cycle kinase inhibitor with selectivity for CDK2, CDK4 and CDK6, giving an IC₅₀ of 1.2 μ M in an *in vitro* assay evaluating its CDK4-inhibitory activity. Potentially useful as an antiproliferative agent for the treatment of cancers, especially solid tumors and leukemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases associated with retinal vessel proliferation.

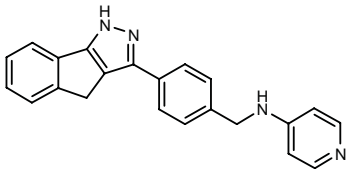
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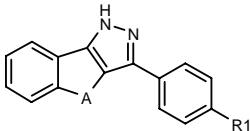
295665

N-[4-(1,4-Dihydroindeno[1,2-*c*]pyrazol-3-yl)benzyl]-N-(4-pyridyl)amine



C22 H18 N4; Mol wt: 338.4122

ACTION – An inhibitor of protein kinases, particularly KDR/FIk-1/VEGFR-2 (vascular endothelial growth factor receptor-2) tyrosine kinases, with potential in the treatment of cancer, arthritis, atherosclerosis, psoriasis, hemangioma, myocardial angiogenesis, coronary and cerebral collateral vascularization, ischemic limb angiogenesis, corneal diseases, neovascular glaucoma, macular degeneration, wounds, ulcers, *Helicobacter*-related diseases, fractures and diabetic retinopathy, as well as burns, chronic lung disease, stroke, polyps, psoriasis, allergic inflammation, ovarian hyperstimulation syndrome and brain tumor-associated cerebral edema. Other specifically claimed compounds from this series of substituted 1,4-dihydroindeno[1,2-*c*]pyrazole derivatives are:



Compound	R1	A	Formula
295666	NHSO2Ph	CH2	C ₂₂ H ₁₇ N ₃ O ₂ S
295667	CONHCH2CH2OMe	CH2	C ₂₀ H ₁₉ N ₃ O ₂
295668	4-NO2-PhNHCO	CH2	C ₂₃ H ₁₈ N ₄ O ₃
295669	1-imidazolyl-CH2CONH	CH2	C ₂₁ H ₁₇ N ₅ O
295670	1-imidazolyl-CH2CH2NH	CH2	C ₂₁ H ₁₉ N ₅
295671	4-morpholinyl-CH2CH2NHSO2	CH2	C ₂₂ H ₂₄ N ₄ O ₃ S
295672	SO2NHCH2CH2OMe	CH2	C ₁₉ H ₁₉ N ₃ O ₃ S
295673	CH2NHCH2CH2N(Me)2	CH2	C ₂₁ H ₂₄ N ₄
295674	SO2NHCH2CH2N(Me)2	CH2	C ₂₀ H ₂₂ N ₄ O ₂ S
295675	4-morpholinyl-CH2CH2NHCH2	CH2	C ₂₃ H ₂₆ N ₄ O
295676	4-EtO-Ph-NHCH2	CH2	C ₂₅ H ₂₃ N ₃ O
295677	2(S)-pyrrolidinyl-CH2NHCO	CH2	C ₂₂ H ₂₂ N ₄ O
295678	1-imidazolyl-(CH2)3NHCH2	S	C ₂₂ H ₂₁ N ₅ S
295679	4-morpholinyl-CH2CH2NHCH2	S	C ₂₂ H ₂₄ N ₄ OS

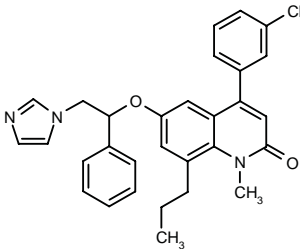
SOURCE – BASF.

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1. Doyle, K.J. et al. (BASF AG) *Substd. 1,4-dihydroindeno[1,2-*c*]pyrazoles as inhibitors of tyrosine kinase.* WO 0059901.

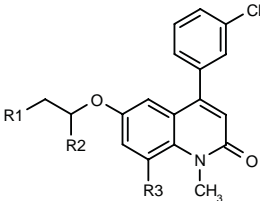
296143

4-(3-Chlorophenyl)-6-[2-(1*H*-imidazol-1-yl)-1-phenyl-ethoxy]-1-methyl-8-propylquinolin-2(1*H*)-one

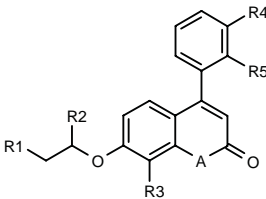


C30 H28 Cl N3 O2; Mol wt: 498.0232

ACTION – Inhibitor of protein farnesyltransferase, potentially useful for the treatment or prevention of cancer, restenosis and atherosclerosis. Other specifically claimed compounds form this series of benzopyranones and quinolones are:



Compound	R1	R2	R3	Formula
296153	1-imidazolyl	Ph	CH2CH2Ph	C ₃₅ H ₃₀ ClN ₃ O ₂
296154	1-(PhCH2)-5-imidazolyl	H	H	C ₂₈ H ₂₄ ClN ₃ O ₂
296155	1-(PhCH2)-5-imidazolyl	H	Pr	C ₃₁ H ₃₀ ClN ₃ O ₂
296156	1-(PhCH2)-5-imidazolyl	H	CH2CH2Ph	C ₃₆ H ₃₂ ClN ₃ O ₂



Compound	R1	R2	R3	R4	R5	A	Formula
296161	1-imidazolyl	Ph	Pr	Cl	H	N(Me)	C ₃₀ H ₂₈ ClN ₃ O ₂
296162	1-imidazolyl	Ph	CH2CH2Ph	Cl	H	N(Me)	C ₃₅ H ₃₀ ClN ₃ O ₂
296164	1-(PhCH2)-5-imidazolyl	H	H	Cl	H	N(Me)	C ₂₈ H ₂₄ ClN ₃ O ₂
296165	1-(PhCH2)-5-imidazolyl	H	Pr	Cl	H	N(Me)	C ₃₁ H ₃₀ ClN ₃ O ₂
296166	1-(PhCH2)-5-imidazolyl	H	CH2CH2Ph	Cl	H	N(Me)	C ₃₆ H ₃₂ ClN ₃ O ₂
296168	1-imidazolyl	Ph	Pr	H	Cl	O	C ₂₉ H ₂₅ ClN ₂ O ₃
296169	1-imidazolyl	Ph	CH2CH2Ph	H	Cl	O	C ₃₄ H ₂₇ ClN ₂ O ₃
296170	1-(PhCH2)-5-imidazolyl	H	H	H	Cl	O	C ₂₇ H ₂₁ ClN ₂ O ₃
296171	1-(PhCH2)-5-imidazolyl	H	Pr	H	Cl	O	C ₃₀ H ₂₇ ClN ₂ O ₃
296173	1-(PhCH2)-5-imidazolyl	H	CH2CH2Ph	H	Cl	O	C ₃₅ H ₂₉ ClN ₂ O ₃

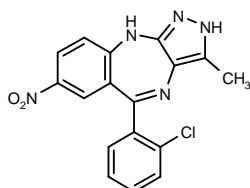
SOURCE – Pfizer.

REFERENCES

1. Kaltenbronn, J.S. et al. (Pfizer Inc.) *Benzopyranone and quinolone inhibitors of ras farnesyl transferase*. US 6143766.

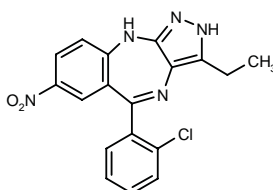
296544

5-(2-Chlorophenyl)-3-methyl-7-nitro-2,10-dihydropyrazolo[3,4-*b*][1,4]benzodiazepine



C17 H12 Cl N5 O2; Mol wt: 353.7678

ACTION – An inhibitor of cyclin-dependent kinases (CDKs), in particular CDK2, with potential in the treatment or control of proliferative disorders, particularly breast, colon, lung and prostate cancer. *In vitro*, compound was shown to inhibit CDK2 activity, as determined by inhibition of purified recombinant retinoblastoma protein phosphorylation ($IC_{50} = 0.01\text{--}0.99\text{ }\mu\text{M}$). In addition, it demonstrated antiproliferative activity in cell-based assays using the estrogen receptor-negative epithelial breast carcinoma MDA-MB-435 and the colon carcinoma SW480 and HCT 116 cell lines, with IC_{50} values in the range $0.01\text{--}1\text{ }\mu\text{M}$. Another compound from this series of pyrazolobenzo-diazepine derivatives is:



296545: C18 H14 Cl N5 O2

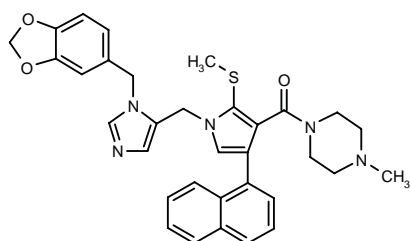
SOURCE – Roche.

REFERENCES

1. Ding, Q. et al. (F. Hoffmann-La Roche AG) *Pyrazolobenzo-diazepines as CDK2 inhibitors*. WO 0064900.

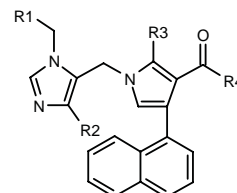
296606

1-[1-[1-(1,3-Benzodioxol-5-ylmethyl)-1*H*-imidazol-5-ylmethyl]-2-(methylsulfanyl)-4-(1-naphthyl)-1*H*-pyrrol-3-yl]-1-(4-methylpiperazin-1-yl)methanone



C33 H33 N5 O3 S; Mol wt: 579.7217

ACTION – Antineoplastic agent, a protein farnesyltransferase inhibitor that is equally effective at inhibiting H-Ras and K-Ras, contrary to previously reported inhibitors. *In vitro*, compound gave IC_{50} values for inhibition of H-Ras and K-Ras enzyme activity of < 0.002 and $< 0.006\text{ }\mu\text{M}$, respectively, and respective CIC_{50} values in a cellular assay of < 0.01 and $< 5\text{ }\mu\text{M}$. Claimed for the treatment or prevention of cancer, restenosis, atherosclerosis and viral infections. Other exemplified compounds from this series of pyrrole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
296607	1,3-benzodioxol-5-yl	H	Me	4-Me-1-Piz	C ₃₃ H ₃₃ N ₅ O ₃
296610	CH ₂ CH ₂ OEt	Me	H	4-Me-1-Piz	C ₃₀ H ₃₇ N ₅ O ₂
296611	CH ₂ CH ₂ OCH ₂ Ph	Me	H	4-Me-1-Piz	C ₃₅ H ₃₉ N ₅ O ₂
296612	CH ₂ CH ₂ OCH ₂ Ph	Me	H	N(Me)CH ₂ CH ₂ OMe	C ₃₄ H ₃₈ N ₄ O ₃
296613	2-Cl-PhCH ₂ OCH ₂ CH ₂	Me	H	4-Me-1-Piz	C ₃₅ H ₃₈ ClN ₅ O ₂

SOURCE – LG Chem.

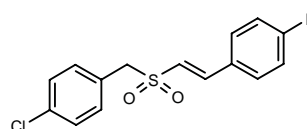
REFERENCES

1. Koh, J.-S. et al. (LG Chem Ltd.) *Farnesyl transferase inhibitors having a pyrrole structure and process for preparation thereof*. WO 0064891.

FRI-20

295473

4-Chlorobenzyl (*E*)-2-(4-fluorophenyl)vinyl sulfone



C15 H12 Cl F O2 S; Mol wt: 310.7748

ACTION – Antineoplastic agent that acts by interfering with the mitogen-activated protein kinase (MAPK) signal transduction pathway, in particular by modulating ERK and JNK kinases. Compound caused $> 95\%$ cell death after 72 h of exposure when tested against breast cancer MCF-7 and BT-20 and prostate cancer LnCaP cell lines at a concentration of $2.5\text{ }\mu\text{M}$, while exhibiting no cytotoxicity against normal murine fibroblast NIH3T3 cells; in addition, it was found to be about 10-fold more potent than cisplatin in killing prostate cancer LnCaP and DU 145 cells *in vitro*. Compound was further shown to arrest cells in the G2/M phase of the cell cycle, and assays using LnCaP and MCF-7 cells showed that it acts by blocking the phosphorylating capacity of ERK2 and enhancing the phosphorylating capacity of JNK.

SOURCE – Temple University, Philadelphia, PA (US).

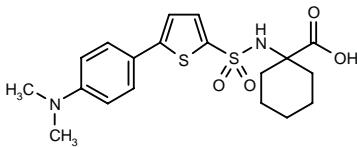
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ANGIOGENESIS INHIBITORS

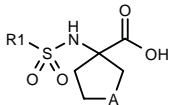
295502

1-[5-[4-(Dimethylamino)phenyl]thien-2-ylsulfonamido]-cyclohexanecarboxylic acid



C19 H24 N2 O4 S2; Mol wt: 408.5406

ACTION – Matrix metalloproteinase MMP-2 (gelatinase A) inhibitor (IC₅₀ = 0.015 μM), potentially useful for the treatment of cancer, nephritis, osteoarthritis, heart failure, rheumatoid arthritis and the like. Other exemplified carbocyclic sulfonamide derivatives are:



Compound	R1	A	Formula
295503	4-[5-(4-Me-Ph)-2-thienyl]-Ph	-(CH2)2-	C ₂₄ H ₂₅ NO ₄ S ₂
295504	5-[4-N(Me)2-Ph]-2-thienyl	-CH2-	C ₁₈ H ₂₂ N ₂ O ₄ S ₂
295505	5-(4-Me-Ph-ethynyl)-2-thienyl	-(CH2)2-	C ₂₀ H ₂₁ NO ₄ S ₂
295506	4-(2-Ph-2H-tetrazol-5-yl)-Ph	-(CH2)2-	C ₂₀ H ₂₁ N ₅ O ₄ S
295507	4-[2-(4-F-Ph)-2H-tetrazol-5-yl]-Ph	-CH2-	C ₁₉ H ₁₈ FN ₅ O ₄ S
295508	4-(5-Ph-1,3,4-oxadiazol-2-yl)-Ph	-(CH2)2-	C ₂₁ H ₂₁ N ₃ O ₅ S

SOURCE – Shionogi.

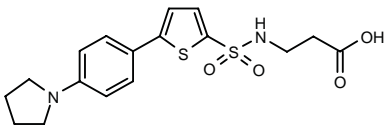
REFERENCES

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295509

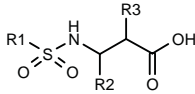
3-[5-[4-(1-Pyrrolidinyl)phenyl]thien-2-ylsulfonamido]-propionic acid

N-[5-[4-(1-Pyrrolidinyl)phenyl]thien-2-ylsulfonyl]-β-alanine



C17 H20 N2 O4 S2; Mol wt: 380.4870

ACTION – Matrix metalloproteinase MMP-2 (gelatinase A) inhibitor (IC₅₀ = 0.00926 μM), potentially useful for the treatment of cancer, nephritis, osteoarthritis, heart failure, rheumatoid arthritis and the like. Other exemplified β-amino acid derivatives are:



Compound	R1	R2	R3	Formula
295510	4-[2-(4-Bu-Ph)-2H-tetrazol-5-yl]-Ph	H	H	C ₂₀ H ₂₃ N ₅ O ₄ S
295511	4-[2-(4-Br-Ph)-2H-tetrazol-5-yl]-Ph	H	H	C ₁₆ H ₁₄ BrN ₅ O ₄ S
295512	4-PhO-Ph	H	H	C ₁₅ H ₁₅ NO ₅ S
295513	5-(4-Me-Ph-ethynyl)-2-thienyl	H	H	C ₁₆ H ₁₅ NO ₄ S ₂
295514	5-[4-N(Me)2-Ph]-2-thienyl	H	H	C ₁₅ H ₁₈ N ₂ O ₄ S ₂
295515	4-[2-(4-Bu-Ph)-2H-tetrazol-5-yl]-Ph	H	Me	C ₂₁ H ₂₅ N ₅ O ₄ S
295516	4-[2-(4-Bu-Ph)-2H-tetrazol-5-yl]-Ph	Ph	H	C ₂₆ H ₂₇ N ₅ O ₄ S

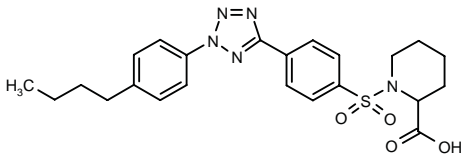
SOURCE – Shionogi.

REFERENCES

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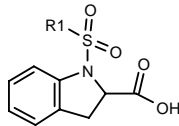
295517

1-[4-[2-(4-Butylphenyl)-2H-tetrazol-5-yl]phenylsulfonyl]-piperidine-2-carboxylic acid

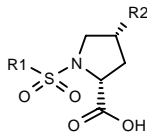


C23 H27 N5 O4 S; Mol wt: 469.5633

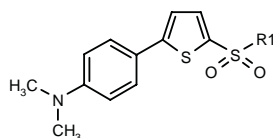
ACTION – Matrix metalloproteinase MMP-2 (gelatinase A) inhibitor (IC₅₀ = 0.00153 μM), potentially useful for the treatment of cancer, nephritis, osteoarthritis, heart failure, rheumatoid arthritis and the like. Other exemplified heterocyclic sulfonamide derivatives are:



Compound	R1	Formula
295518	4-[2-(4-Bu-Ph)-2H-tetrazol-5-yl]-Ph	C ₂₆ H ₂₆ N ₅ O ₄ S
295525	5-[4-N(Me)2-Ph]-2-thienyl	C ₂₁ H ₂₀ N ₂ O ₄ S ₂



Compound	R1	R2	Formula
295519	4-[2-(4-Bu-Ph)-2H-tetrazol-5-yl]-Ph	H	C ₂₂ H ₂₅ N ₅ O ₄ S
295520	4-[2-(4-MeO-Ph)-2H-tetrazol-5-yl]-Ph	OH	C ₁₉ H ₁₉ N ₅ O ₆ S
295521	5-(4-Me-Ph-ethynyl)-2-thienyl	H	C ₁₈ H ₁₇ NO ₄ S ₂
295522	5-(4-Me-Ph-ethynyl)-2-thienyl	OH	C ₁₈ H ₁₇ NO ₅ S ₂
295524	5-(4-Me-Ph)-2-thienyl	OH	C ₁₆ H ₁₇ NO ₅ S ₂



Compound	R1	Formula
295523	3-CO ₂ H-1,2,3,4-tetrahydro-2-isoquinolyl	C ₂₂ H ₂₂ N ₂ O ₄ S ₂
295526	3-CO ₂ H-1-Pip	C ₁₈ H ₂₂ N ₂ O ₄ S ₂

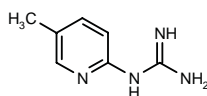
SOURCE – Shionogi.

REFERENCES

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295707

N-(5-Methylpyridin-2-yl)guanidine



C₇ H₁₀ N₄; Mol wt: 150.1840

ACTION – Potent, reversible and competitive inhibitor of urokinase (urinary-type plasminogen activator, or uPA) with selectivity relative to certain other proteases such as tissue-type plasminogen activator (tPA) and plasmin. Potentially useful for the treatment of conditions mediated by uPA such as angiogenesis, bone restructuring, embryo implantation in the uterus, infiltration of immune cells into inflammatory sites, ovulation, spermatogenesis, tissue remodeling during wound repair and organ differentiation, fibrosis, local invasion of tumors into adjacent areas, metastatic spread of tumor cells from primary to secondary sites, psoriasis and tissue destruction in arthritis. A representative compound from a series of 2-pyridinylguanidines.

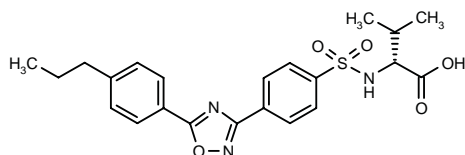
SOURCE – Pfizer.

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1. Barber, C.G. and Dickinson, R.P. (Pfizer Inc.;Pfizer Ltd.) *2-Pyridinylguanidine urokinase inhibitors.* EP 1044967, JP 2000297074.

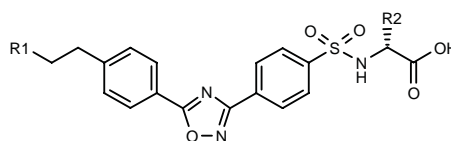
296177

N-[4-[5-(4-Propylphenyl)-1,2,4-oxadiazol-3-yl]phenyl-sulfonyl]-D-valine



C₂₂ H₂₅ N₃ O₅ S; Mol wt: 443.5215

ACTION – Matrix metalloproteinase (MMP) inhibitor with an IC₅₀ of 0.883 nM when tested for inhibition of MMP-2 (gelatinase A). Expected to be of use for the treatment of cancer, nephritis, osteoarthritis, heart failure, rheumatoid arthritis, etc. Other exemplified sulfonamide derivatives are:



Compound	R1	R2	Formula
296178	H	i-Pr	C ₂₁ H ₂₃ N ₃ O ₅ S
296179	Et	i-Pr	C ₂₃ H ₂₇ N ₃ O ₅ S
296180	Me	Me	C ₂₀ H ₂₁ N ₃ O ₅ S
296181	H	3-indolyl-CH ₂	C ₂₇ H ₂₄ N ₄ O ₅ S
296183	Me	3-indolyl-CH ₂	C ₂₈ H ₂₆ N ₄ O ₅ S

SOURCE – Shionogi.

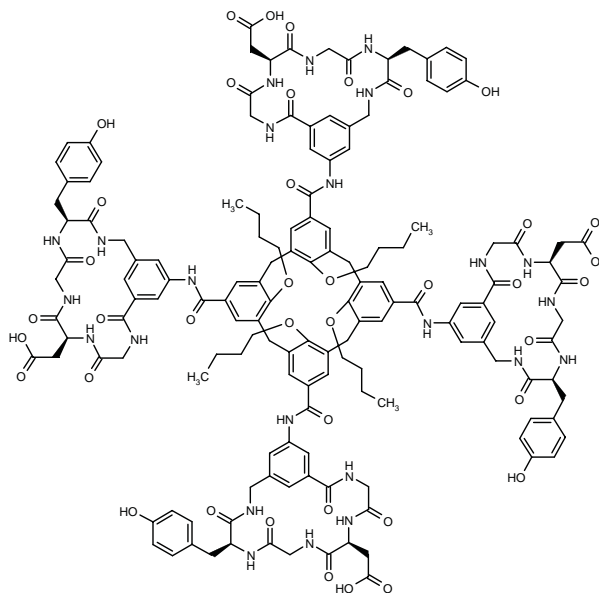
REFERENCES

1. Watanabe, F. et al. (Shionogi & Co. Ltd.) *Sulfonamide derivs. having oxadiazole rings.* WO 0063194.

GFB-111

287658

1,1',1'',1'''-[[25,26,27,28-Tetrabutoxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19,(26),21,23-dodecaene-5,11,17,23-tetrayl]tetrakis[carbonylimino[5-(aminomethyl)-3,1-phenylene]carbonyl]]tetrakis[glycyl-L-α-aspartyl-glycyl-L-tyrosine] (4→1),(4'→1''),(4''→1'''),(4'''→1''')-tetra-lactam



C₁₄₈ H₁₆₀ N₂₄ O₄₀; Mol wt: 2915.0200

Light yellow powder, m.p. > 350 °C.

ACTION – Antiangiogenic agent proven to selectively bind platelet-derived growth factor (PDGF) and inhibit PDGF-BB-stimulated PDGF receptor tyrosine phosphorylation ($IC_{50} = 250$ nM), while having no activity ($IC_{50} > 100$ μ M) against epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF) and heregulin β (HRG β); compound inhibited vascular endothelial growth factor (VEGF)-induced Flk-1 tyrosine phosphorylation and ERK1/ERK2 activation with an IC_{50} of 10 μ M. In nude mice bearing human brain cancer U-87 MG xenografts, human lung carcinoma A549 xenografts or rat glial cell cancer C6, compound at a dose of 50 mg/kg/day i.p. significantly inhibited tumor growth and angiogenesis.

SOURCES – University of South Florida, Tampa, FL (US); Yale University, New Haven, CT (US).

REFERENCES

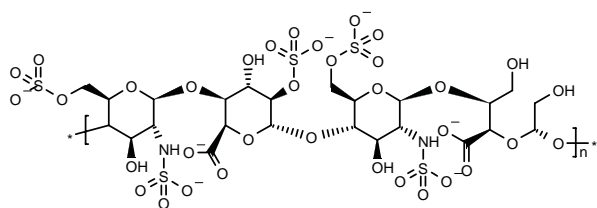
1. Blaskovich, M.A. et al. *Design of GFB-111, a platelet-derived growth factor binding molecule with antiangiogenic and anticancer activity against human tumors in mice*. Nat Biotechnol 2000, 18(10): 1065.
2. Park, H.S. et al. *Protein surface recognition by synthetic receptors: A route to novel submicromolar inhibitors for α -chymotrypsin*. J Am Chem Soc 1999, 121(1): 8.
3. Sebt, S.M. et al. *A platelet-derived growth factor binding molecule, GFB-111, inhibits angiogenesis and tumor growth of human tumors in mice*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3366.

ST-1646

296095

Poly[*O*-(2-deoxy-6-*O*-sulfo-2-(sulfoamino)- β -D-glucopyranosyl)-(1-4)-*O*-(2-*O*-sulfo- α -L-idopyranosyl-uronic acid)-(1-4)-*O*-(2-deoxy-6-*O*-sulfo-2-(sulfoamino)- β -D-glucopyranosyl)-(1-4)-*O*-(2,3-seco- α -L-idopyranosyl-uronic acid)]

p-PST.sU



(C24 H33 N2 O35 S5)_n; Mol wt: 1069.8340

ACTION – Heparin derivative consisting of pentasulfated trisaccharide (PST) sequences containing the minimal basic fibroblast growth factor (FGF2)-binding sequence of heparin. Compared with heparin, compound lacks the anticoagulant activity but retains the FGF2-binding activity. It showed a reduced ability to induce FGF2 dimerization and was more effective in inhibiting FGF2-induced mitogenesis in cultured endothelial cells. In addition, this novel derivative exhibited significant antiangiogenic activity in the chick embryo chorioallantoic membrane (CAM) assay and represents a useful lead in the development of novel agents for angiogenic disorders and solid tumors.

SOURCE – Sigma-Tau.

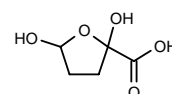
REFERENCES

1. Casu, B. et al. *Novel heparin derivative that prevents dimerization of FGF-2 and inhibits angiogenesis*. Clin Cancer Res 2000, 6(Suppl.): Abst 276.

OTHER ONCOLYTIC DRUGS

295292

2,5-Dihydroxytetrahydrofuran-2-carboxylic acid



C5 H8 O5; Mol wt: 148.1132

ACTION – Antineoplastic and antibacterial agent obtained by subjecting glucaric acid (saccharic acid) to heat treatment.

SOURCE – Takara Shuzo.

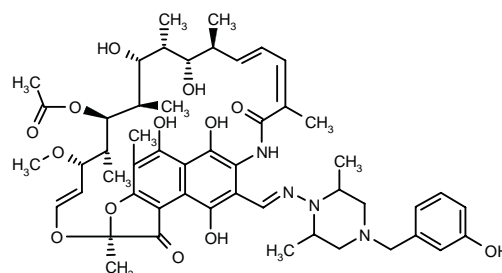
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296126

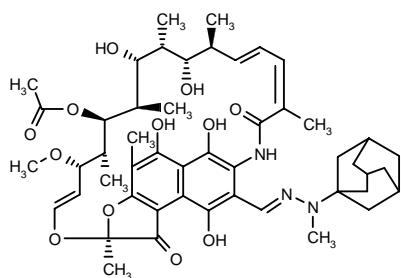
3-[4-(3-Hydroxybenzyl)-2,6-dimethylpiperazin-1-yliminomethyl]rifamycin SV

(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-21-Acetoxy-5,6,9,17,19-tetrahydroxy-8-[4-(3-hydroxybenzyl)-2,6-dimethylpiperazin-1-yliminomethyl]-23-methoxy-2,4,12,16,18,20,22-heptamethyl-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-*b*]furan-1,11-dione



C51 H66 N4 O13; Mol wt: 943.0974

ACTION – Heregulin (HRG) antagonist with potential for the treatment of cancer, particularly breast cancer. Compound was shown to exhibit high specificity, inhibiting only HRG-dependent cell growth in murine hematopoietic 32D cells transfected with the erbB4 receptor but not IL-3-stimulated growth in 32D or 32D/erbB4 cells. In addition, it potently inhibited soft agar colony formation in breast cancer MDA-231 cells at 20 μ M, and was shown to inhibit the binding of the [125 I]-labeled EGF domain of HRG β 1 (HED- β 1) to its receptors in T47D or MDA-453 cells, as well as HRG-induced tyrosine phosphorylation in T47D cells. Another compound from this series of rifamycin analogues is:



296127: C₄₉ H₆₅ N₃ O₁₂

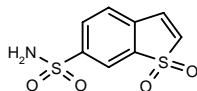
SOURCE – Georgetown University, Washington, DC (US).

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1. Yang, D. et al. (Georgetown University) *Heregulin antagonists and methods for their use*. US 6143740, WO 9821956.

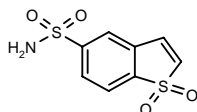
296392

1,1-Dioxo-1*H*-1-benzo[*b*]thiophene-6-sulfonamide



C₈ H₇ N O₄ S₂; Mol wt: 245.2783

ACTION – Antineoplastic agent, particularly useful for the treatment of carcinomas and other solid tumors, that acts by inhibiting NADH oxidase activity and inducing apoptosis. Its tumor growth-inhibitory activity was demonstrated in human colon HT-29, lung HTB54, melanoma M13443, leukemia K-562 and leukemia CCRF-CEM cancer cells by cell growth inhibition in the range 45-96% at 1-100 μ M. Another exemplified benzo[*b*]thiophene-sulfonamide 1,1-dioxide derivative is:



296393: C₈ H₇ N O₄ S₂

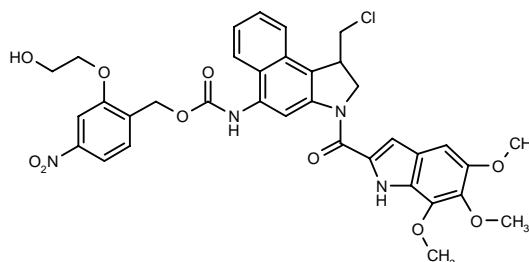
SOURCE – Universidad Pública de Navarra, Pamplona (ES).

REFERENCES

1. Martinez Merino, V. et al. (Universidad Pública de Navarra) *Benzo[*b*]thiophene sulfonamide-1,1-dioxide derivs. and their use as antineoplastic agents*. WO 0063202.

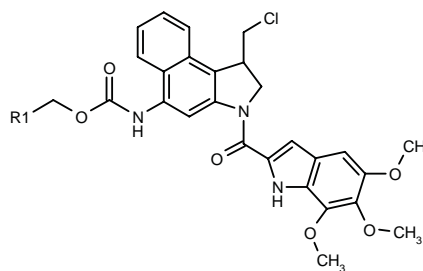
296559

1-(Chloromethyl)-3-(5,6,7-trimethoxy-1*H*-indol-2-ylcarbonyl)-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamic acid 2-(2-hydroxyethoxy)-4-nitrobenzyl ester



C₃₅ H₃₃ Cl N₄ O₁₀; Mol wt: 705.1167

ACTION – Prodrug that is converted to a cytotoxic agent following activation by reduction of the nitro groups by nitroreductases and is thus expected to be useful in conjunction with nitroreductase enzymes for the ADEPT (antibody-directed enzyme/prodrug therapy) or GDEPT (gene-directed enzyme prodrug therapy) therapy of cancers, in particular solid tumors such as breast, colon and lung tumors. *In vitro*, compound exhibited potent cytotoxicity following activation by nitroreductases, as demonstrated in several pairs of mammalian cell lines (wild type [WT] and nitroreductase-positive transfectants [NR+]), giving IC₅₀ ratios (WT/NR+) of 84 (human ovarian cancer SK-OV-3/SC3.2), 147 (human colon cancer WiDr/WC14.10) and 104 (murine mammary carcinoma EMT6-V/EN2A). Other exemplified compounds from this series of nitroaromatic carbamate prodrugs of amino derivatives include the following:



Compound	R1	Formula
296560	2-(MeOCH ₂ CH ₂ O)-4-NO ₂ -Ph	C ₃₆ H ₃₅ ClN ₄ O ₁₀
296561	2-[HO(CH ₂) ₃ O]-4-NO ₂ -Ph	C ₃₆ H ₃₅ ClN ₄ O ₁₀
296562	1-Me-5-NO ₂ -2-imidazolyl	C ₃₁ H ₂₉ ClN ₆ O ₈

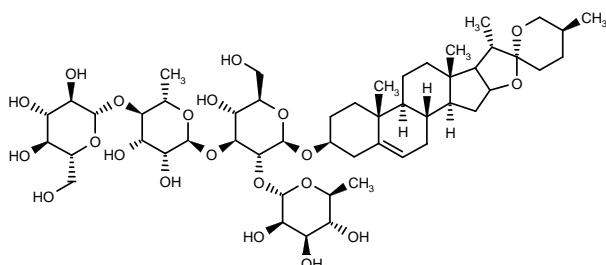
SOURCE – Cancer Research Campaign Technology.

REFERENCES

1. Denny, W.A. et al. (Cancer Research Campaign Technology Ltd.) *N-Protected amines and their use as prodrugs*. WO 0064864.

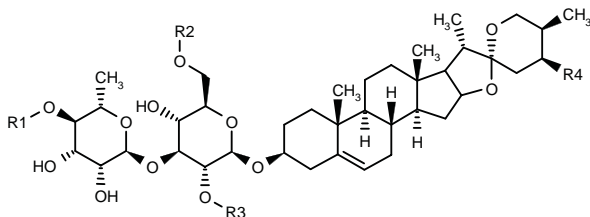
296586

(25*S*)-3-β-[3-*O*-[6-Deoxy-4-*O*-(β-D-glucopyranosyl)-α-L-mannopyranosyl]-2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyloxy]-5-spirosten

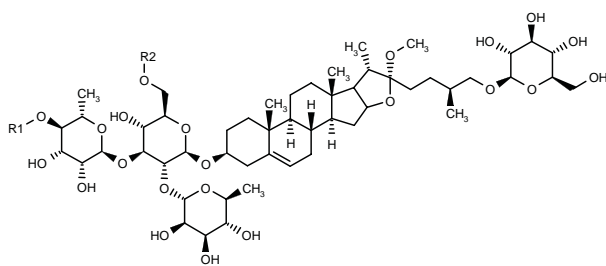


C51 H82 O21; Mol wt: 1031.1880

ACTION – Antineoplastic agent prepared by chemical synthesis or extracted from the plant *Tacca esquirolii*, proven to inhibit the proliferation of human acute promyeloid leukemia HL-60 cells with an IC₅₀ value of 1.9 μg/ml. Other exemplified compounds from this series of sugar-substituted steroid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
296587	β-D-glucopyranosyl	H	H	H	C ₄₅ H ₇₂ O ₁₇
296588	H	H	6-deoxy-α-L-mannopyranosyl	OH	C ₄₅ H ₇₂ O ₁₇
296589	β-D-glucopyranosyl	H	6-deoxy-α-L-mannopyranosyl	OH	C ₅₁ H ₈₂ O ₂₂
296590	β-D-glucopyranosyl	Ac	6-deoxy-α-L-mannopyranosyl	H	C ₅₃ H ₈₄ O ₂₂



Compound	R1	R2	Formula
296591	beta-D-glucopyranosyl	H	C ₅₈ H ₉₆ O ₂₇
296592	beta-D-glucopyranosyl	Ac	C ₆₀ H ₉₈ O ₂₈
296593	H	H	C ₅₂ H ₈₆ O ₂₂

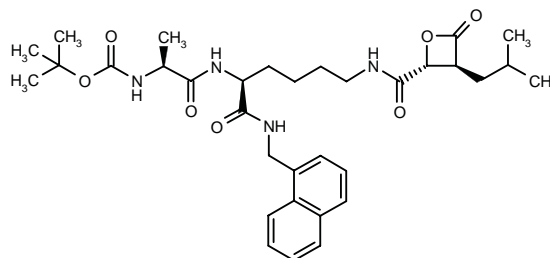
SOURCE – Kaneka.

REFERENCES

- Sashida, Y. et al. (Kaneka Corp.) *Cell proliferation inhibitors*. JP 2000239296.

296981

N-(*tert*-Butoxycarbonyl)-L-alanyl-*N*⁶-[3(*S*)-(2-methylpropyl)-4-oxooxetan-2(*R*)-ylcarbonyl]-*N*¹-(1-naphthylmethyl)-L-lysineamide



C33 H46 N4 O7; Mol wt: 610.7474

ACTION – Belactosin derivative with antitumor activity due to selective proteasome inhibition, being more potent than belactosin A (IC₅₀ = 1.0 nM vs. 400 nM).

SOURCE – Kyowa Hakko.

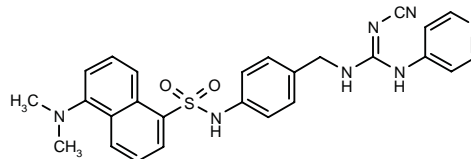
REFERENCES

- Yamaguchi, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Proteasome inhibitors*. WO 0043000.
- Yamaguchi, H. et al. *Synthesis of belactosin derivatives, novel proteasome inhibitors*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 1P-12.

SBR-11-2897

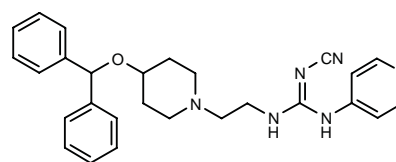
295817

N-[4-[2-Cyano-3-(4-pyridyl)guanidinomethyl]phenyl]-5-(dimethylamino)naphthalene-1-sulfonamide



C26 H25 N7 O2 S; Mol wt: 499.5965

ACTION – Antineoplastic agent with high specificity for tumor cells and potent activity when tested in nude mice bearing non-Hodgkin's B-cell lymphoma xenografts, producing an almost complete reduction in average tumor volumes relative to controls at 20 mg/kg b.i.d. (one dose i.v. and the other dose i.p.). No mortality was observed following single doses of 200 mg/kg i.v. Another compound from this series of cyanoguanidine derivatives is:



SBR-11-4483 [295819]: C27 H30 N6 O

SOURCE – Shionogi.

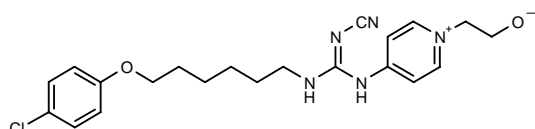
REFERENCES

1. Huang, T.-N. et al. (Shionogi BioResearch Corp.) *Cyanoguanidine cpds.* WO 0061561.

SBR-11-3702

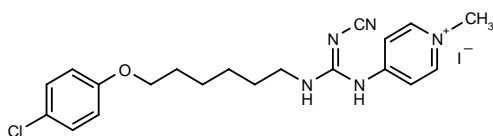
295815

2-[4-[3-[6-(4-Chlorophenoxy)hexyl]-2-cyanoguanidino]-pyridinium-1-yl]ethan-1-olate



C₂₁ H₂₆ Cl N₅ O₂; Mol wt: 415.9224

ACTION – Antineoplastic agent with high specificity for tumor cells and low toxicity. Another specifically claimed compound from this series of *N*-substituted cyanoguanidine derivatives is:



SBR-11-3551 [295816]: C₂₀ H₂₅ Cl I N₅ O

SOURCE – Shionogi.

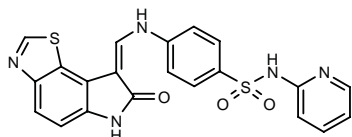
REFERENCES

1. Huang, T.-N. et al. (Shionogi BioResearch Corp.) *N-Substd. cyanoguanidine cpds.* WO 0061559.

CHEMOPROTECTIVE AGENTS

297928

4-[(Z)-(7-Oxo-7,8-dihydro-6*H*-thiazolo[5,4-*e*]indol-8-ylidene)methylamino]-*N*-(2-pyridyl)benzenesulfonamide



C₂₁ H₁₅ N₅ O₃ S₂; Mol wt: 449.5135

ACTION – Potential agent for the prevention of chemotherapy-induced alopecia, a potent cyclin-dependent kinase CDK2 inhibitor (IC₅₀ = 10 nM) with selectivity relative to other CDKs and protein kinases (IC₅₀ > 100 nM). Studies using human fibroblasts showed that it protects cells from cytotoxic agents and inhibits cell cycle progression in the S phase in a reversible manner, without inducing apoptosis. It was able to inhibit etoposide-induced apoptosis in human fibroblasts and to reduce the cytotoxicity of a range of other anticancer agents in mink

lung epithelial CCL64 cells. In a neonatal rat model of chemotherapy-induced alopecia, compound prevented hair loss at the administration site in 33-50% of the animals, without exhibiting toxicity to the normal epithelium. It did not appear to reduce the antitumor activity of cytotoxic agents.

SOURCE – GlaxoSmithKline.

REFERENCES

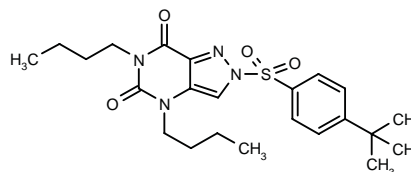
1. Davis, S.T. et al. (Glaxo Group Ltd.) *Substd. oxindole derivs. as protein tyrosine kinase and as protein serine/threonine kinase inhibitors.* EP 1009738, WO 9915500.
2. Davis, S.T. et al. *Prevention of chemotherapy-induced alopecia in rats by CDK inhibitors.* Science 2001, 291(5501): 134.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

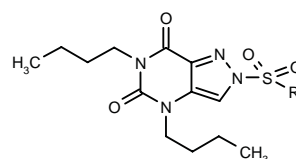
295317

4,6-Dibutyl-2-(4-*tert*-butylphenylsulfonyl)-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-dione



C₂₃ H₃₂ N₄ O₄ S; Mol wt: 460.5958

ACTION – Agent for the treatment of disorders associated with bone loss, particularly Paget's disease, postmenopausal osteoporosis, senile osteoporosis and glucocorticoid-induced osteoporosis, that acts by inducing the expression and release of endogenous calcitonin, as demonstrated *in vitro* in a calcitonin/luciferase reporter gene expression assay in C1-3 cells (derived from human thyroid carcinoma TT cells by stable transfection with a single copy of a calcitonin/luciferase reporter gene) and in an RIA assay in C1-3 cells. In addition, compound was found to produce a 101% increase in plasma calcitonin levels when administered to rats at a dose of 30 mg/kg/day b.i.d. s.c. Other exemplified compounds from this series of pyrazolopyrimidine-2,4-dione sulfonamides are:



Compound	R1	Formula
295318	2-Naph	C ₂₃ H ₂₆ N ₄ O ₄ S
295319	4,5-(Cl)2-2-thienyl	C ₁₇ H ₂₀ Cl ₂ N ₄ O ₄ S ₂
295320	5-Cl-1,3-(Me)2-4-pyrazolyl	C ₁₈ H ₂₅ ClN ₆ O ₄ S

SOURCE – Shionogi.

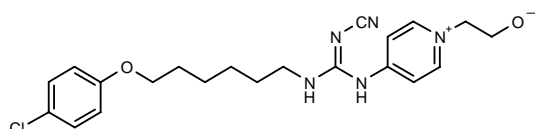
REFERENCES

1. Huang, T.-N. et al. (Shionogi BioResearch Corp.) *Cyanoguanidine cpds.* WO 0061561.

SBR-11-3702

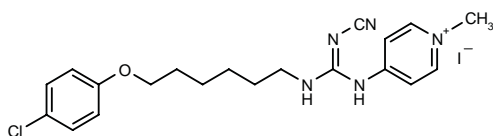
295815

2-[4-[3-[6-(4-Chlorophenoxy)hexyl]-2-cyanoguanidino]-pyridinium-1-yl]ethan-1-olate



C₂₁ H₂₆ Cl N₅ O₂; Mol wt: 415.9224

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SBR-11-3551 [295816]: C₂₀ H₂₅ Cl I N₅ O

SOURCE – Shionogi.

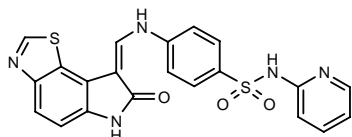
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lung epithelial CCL64 cells. In a neonatal rat model of chemotherapy-induced alopecia, compound prevented hair loss at the administration site in 33-50% of the animals, without exhibiting toxicity to the normal epithelium. It did not appear to reduce the antitumor activity of cytotoxic agents.

SOURCE – GlaxoSmithKline.

REFERENCES

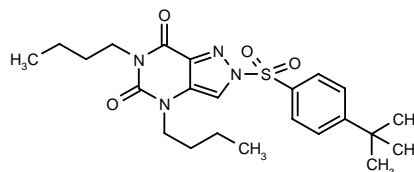
1. Davis, S.T. et al. (Glaxo Group Ltd.) *Substd. oxindole derivs. as protein tyrosine kinase and as protein serine/threonine kinase inhibitors.* EP 1009738, WO 9915500.
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

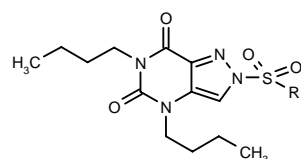
295317

4,6-Dibutyl-2-(4-*tert*-butylphenylsulfonyl)-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-dione



C₂₃ H₃₂ N₄ O₄ S; Mol wt: 460.5958

ACTION – Agent for the treatment of disorders associated with bone loss, particularly Paget's disease, postmenopausal osteoporosis, senile osteoporosis and glucocorticoid-induced osteoporosis, that acts by inducing the expression and release of endogenous calcitonin, as demonstrated *in vitro* in a calcitonin/luciferase reporter gene expression assay in C1-3 cells (derived from human thyroid carcinoma TT cells by stable transfection with a single copy of a calcitonin/luciferase reporter gene) and in an RIA assay in C1-3 cells. In addition, compound was found to produce a 101% increase in plasma calcitonin levels when administered to rats at a dose of 30 mg/kg/day b.i.d. s.c. Other exemplified compounds from this series of pyrazolopyrimidine-2,4-dione sulfonamides are:



Compound	R1	Formula
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295320	5-Cl-1,3-(Me)2-4-pyrazolyl	C ₁₈ H ₂₅ ClN ₆ O ₄ S

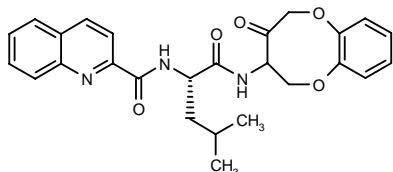
SOURCE – American Home Products.

REFERENCES

1. Gilbert, A.M. et al. (American Home Products Corp.) *Pyrazolopyrimidine-2,4-dione sulfonamides*. US 6133273.

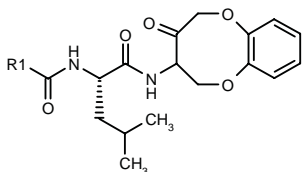
295409

N^α-(2-Quinolylcarbonyl)-L-leucine (4-oxo-2,3,4,5-tetrahydro-1,6-benzodioxocin-3-yl)amide



C26 H27 N3 O5; Mol wt: 461.5153

ACTION – Protease inhibitor, particularly cathepsin K inhibitor, potentially useful for the treatment of diseases associated with excessive bone or cartilage loss such as osteoporosis, gingivitis, periodontitis, arthritis, Paget's disease, hypercalcemia of malignancy and metabolic bone disease. Other specifically claimed 4-amino-4,5-dihydrobenzo[*b*][1,4]dioxocin-3-one derivatives are:



Compound	R1	Formula
295410	2-benzofuryl	C ₂₅ H ₂₆ N ₂ O ₆
295411	2-Naph	C ₂₇ H ₂₈ N ₂ O ₅
295412	2-benzothieryl	C ₂₆ H ₂₆ N ₂ O ₅ S
295413	5-(4-morpholinyl-CH ₂ CH ₂ O)-2-benzofuryl	C ₃₁ H ₃₇ N ₃ O ₈
295414	5-(3-CF ₃ -Ph)-2-furyl	C ₂₈ H ₂₇ F ₃ N ₂ O ₆

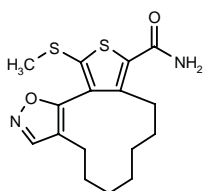
SOURCE – GlaxoSmithKline.

REFERENCES

1. Yamashita, D.S. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 0058296.

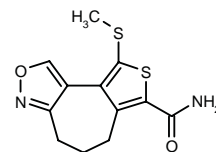
296615

13-(Methylsulfanyl)-5,6,7,8,9,10-hexahydro-4*H*-thieno-[3',4':3,4]cycloundeca[1,2-*d*]isoxazole-11-carboxamide



C16 H20 N2 O2 S2; Mol wt: 336.4780

ACTION – Osteogenesis-promoting agent for the treatment of osteoporosis and other bone disorders, also reported to be useful for the treatment of neuronal disorders. Another exemplified compound from this series of tricyclic thiophene derivatives is:



296616: C12 H12 N2 O2 S2

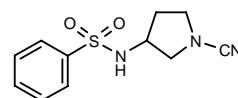
SOURCE – Taisho.

REFERENCES

1. Saito, H. et al. (Taisho Pharmaceutical Co., Ltd.) *Tricyclic thiophene cpds*. JP 2000239280.

297903

N-(1-Cyano-3-pyrrolidiny)benzenesulfonamide



C11 H13 N3 O2 S; Mol wt: 251.3087

ACTION – Potent and reversible cathepsin K and L inhibitor (IC₅₀ = 0.05 and 0.08 μM, respectively), also active in a gelatinase assay (IC₅₀ = 0.018 μM). In an *in vitro* model of bovine bone resorption induced by rabbit osteoclasts, compound inhibited bone resorption with an IC₅₀ value of 0.75 μM. It exhibited a good pharmacokinetic profile in rats after i.v. and oral administration, with a half-life of 2 h (after i.v. dosing in PEG-200/water) and an oral bioavailability of 38%. Selected for further studies as a potential treatment for diseases involving excessive bone resorption.

SOURCES – Axy's Pharmaceuticals; Merck & Co.; Merck Frosst.

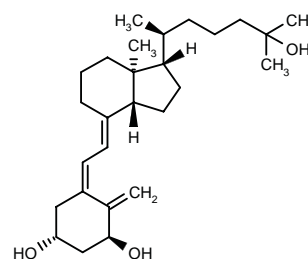
REFERENCES

1. Falgoutret, J.-P. et al. *Novel, nonpeptidic cyanamides as potent and reversible inhibitors of human cathepsins K and L*. J Med Chem 2001, 44(1): 94.

298507

(1*S*,3*R*,5*Z*,7*E*,13*S*,14*S*,17*S*,20*S*)-9,10-Secocholesta-5,7,10-triene-1,3,25-triol

(1*S*,13*S*,14*S*,17*S*,20*S*)-1,25-Dihydroxyvitamin D₃



C27 H44 O3; Mol wt: 416.6416

ACTION – Vitamin D analogue with significant binding affinity for the vitamin D receptor and weak agonist activity in cellular systems, where it induced differentiation of HL-60 cells to monocytes and inhibited human peripheral blood mononuclear cell (PBMC) proliferation at doses above 100 nM. Compound was much better tolerated in mice than 1 α ,25-dihydroxyvitamin D₃ and did not affect serum calcium levels at a dose of 10 μ g/kg. Potentially useful for the treatment of bone diseases.

SOURCES – Polish Academy of Science, Kraków (PL); Schering AG.

REFERENCES

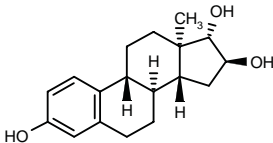
1. Achmatowicz, B. et al. *The first synthesis and biological testing of the enantiomer of 1 α ,25-dihydroxyvitamin D₃*. Tetrahedron Lett 2001, 42(15): 2891.

2. Marczak, S. et al. *Synthesis and biological activity of the 1 α ,25-dihydroxyvitamin D₃ diastereomer with unnatural configuration at the rings C/D side-chain moiety*. Bioorg Med Chem Lett 2001, 11(1): 63.

ent-ESTRIOL

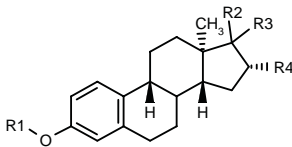
296423

ent-Estra-1,3,5(10)-triene-3,16 β ,17 α -triol

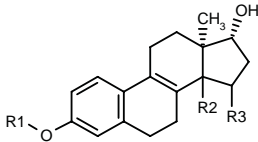


C18 H24 O3; Mol wt: 288.3846

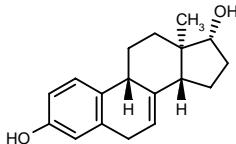
ACTION – Tissue-selective estrogen with higher affinity for rat prostatic than for rat uterine estrogen receptors. It also exhibited higher potency in protecting against bone mass loss than in stimulating uterus weight in ovariectomized rats. The compound is indicated in hormone replacement therapy (HRT) for alleviating peri- and postmenopausal symptoms and for the treatment or prevention of bone mass loss, osteoporosis, atherosclerosis, rheumatoid arthritis, benign prostatic hyperplasia, male and female infertility, among others. Other specifically claimed *ent*-steroids are:



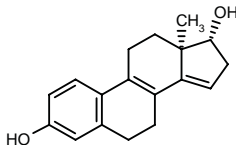
Compound	R1	R2	R3	R4	Isomer	Formula
296424	SO2NHAc	-O-	H			C ₂₀ H ₂₆ NO ₅ S
296425	SO2N(Me)2	OH	H	H	17 α	C ₂₀ H ₂₉ NO ₄ S
296426	SO2NH2	-O-	OH			C ₁₈ H ₂₃ NO ₅ S
296427	H	H	H	OH		C ₁₈ H ₂₄ O ₂
296432	H	-O-	OH			C ₁₈ H ₂₂ O ₃



Compound	R1	R2,R3	Isomer	Formula
296428	SO2NHAc	-CH2-	14 α ,15 α	C ₂₁ H ₂₆ NO ₅ S
296429	H	H,H	14 β	C ₁₈ H ₂₂ O ₂



296430: C18 H22 O2



296431: C18 H20 O2

SOURCE – Schering AG.

REFERENCES

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MAB P112-4C1

299128

Complex-specific anti- $\alpha_v\beta_3$ integrin monoclonal antibody

ACTION – Anti- $\alpha_v\beta_3$ integrin monoclonal antibody proven to inhibit Mn-induced binding of melanoma M21 cells to fibrinogen and migration of these cells to fibrinogen. It also inhibited 293/B3 cell adhesion to vitronectin and rabbit osteoclast adhesion to osteopontin. Potentially useful for the treatment of osteoporosis, hypercalcemia of malignancy, atherosclerosis, restenosis, ocular neovascularization, macular degeneration, diabetic retinopathy, psoriasis and rheumatoid arthritis. Other specifically claimed antibodies are:

MAB P113-7D6 [299130]

MAB P113-12A6 [299131]

MAB P112-11D2 [299132]

MAB P112-10D4 [299133]

MAB P113-1F3 [299134]

SOURCE – Pharmacia.

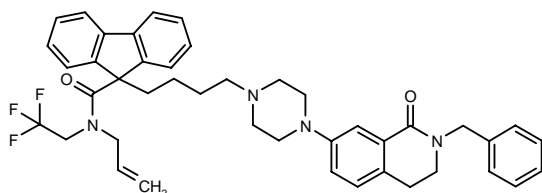
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1. Carron, C.P. et al. (Pharmacia Corp.) *Anti- $\alpha_v\beta_3$ integrin antibody antagonists*. US 6171588.

TREATMENT OF LIPOPROTEIN DISORDERS

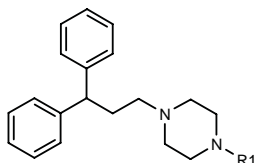
295957

N-Allyl-9-[4-[4-(2-benzyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)piperazin-1-yl]butyl]-*N*-(2,2,2-trifluoroethyl)-9*H*-fluorene-9-carboxamide



C43 H45 F3 N4 O2; Mol wt: 706.8485

ACTION – Hypolipidemic agent that inhibits the biosynthesis of triglycerides in the liver and the secretion of apolipoprotein B (apoB), as demonstrated in HepG2 cells (89 and 80% inhibition, respectively, at 1 μ M). Potentially useful for the treatment of hyperlipidemia, atherosclerosis and pancreatitis without the side effect of fat accumulation in the liver. Other exemplified nitrogen-containing heterocyclic compounds are:



Compound	R1	Formula
295958	2-PhCH2-1-oxo-1,2,3,4-tetrahydro-2,6-naphthyridin-7-yl	C ₃₄ H ₃₆ N ₄ O
295959	2-PhCH2-1-oxo-1,2-dihydro-7-phthalazinyl	C ₃₄ H ₃₄ N ₄ O

SOURCE – Meiji Seika.

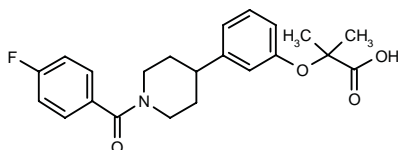
REFERENCES

1. Ohkura, N. et al. (Meiji Seika Kaisha, Ltd.) *Nitrogen-containing heterocyclic cpds. and benzamide cpds. and drugs containing the same*. WO 0061556.

AHL-157*

215169

2-[3-[1-(4-Fluorobenzoyl)piperidin-4-yl]phenoxy]-2-methylpropionic acid



C22 H24 F N O4; Mol wt: 385.4390

ACTION – Lipid-lowering fibrate found to strongly reduce total cholesterol and triglyceride levels (37 and 34%, respectively) when mixed in the diet at 0.003% to rats fed a high-cholesterol diet. In genetically obese diabetic KKA^y mice, compound mixed in the diet at 0.03% reduced blood glucose and triglyceride levels by 25 and 32%, respectively.

SOURCES – Arena; SSP.

REFERENCES

1. Komoto, T. et al. (SSP Co., Ltd.) *Arylamide derivs*. EP 0607536, JP 1995053517, US 5411972.

2. Komoto, T. et al. *New strong fibrates with piperidine moiety*. Chem Pharm Bull 2000, 48(12): 1978.

3. Komoto, T. et al. *Preparation of new fibrates with piperidine ring and the pharmacological activity*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 2P-06.

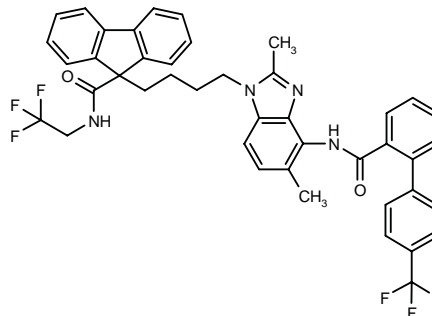
4. *SS Pharm. outlicenses drug candidates to speed development, reduce costs*. DailyDrugNews.com (Daily Essentials) 1999, March 3.

*Identified compound **215169** (see **213768**) Drug Data Rep 1995, 017(01): 0102.

BMS-212122

295392

9-[4-[2,5-Dimethyl-4-[4'-(trifluoromethyl)biphenyl-2-ylcarboxamido]-1*H*-benzimidazol-1-yl]butyl]-*N*-(2,2,2-trifluoroethyl)-9*H*-fluorene-9-carboxamide



C43 H36 F6 N4 O2; Mol wt: 754.7714

ACTION – Microsomal triglyceride transfer protein (MTP) inhibitor (IC₅₀ = 1 nM) proven to inhibit the secretion of apolipoprotein B in HepG2 cells (IC₅₀ = 0.03 nM), being 8-26-fold more potent than the parent compound BMS-201038 (IC₅₀ = 8 and 0.8 nM, respectively). *In vivo*, it induced a significant decrease in plasma triglyceride levels in hamsters fed a standard diet (ED₅₀ = 0.28 mg/kg/day p.o. for 3 days), and it also induced a dose-dependent (0.1-1 mg/kg) decrease in total cholesterol, VLDL/LDL and HDL cholesterol levels (37, 51 and 18%, respectively, at 0.1 mg/kg/day for 3 days). Moreover, in cynomolgus monkeys, compound induced a strong decrease in plasma triglycerides, total cholesterol, VLDL/LDL and HDL cholesterol (71, 73, 84 and 68%, respectively, at 1 mg/kg p.o.). In all *in vivo* tests it was significantly more potent than BMS-201038 in reducing plasma lipids. Compound showed good oral bioavailability in rats (81%) and moderate oral bioavailability in monkeys (23%). Potentially useful for the treatment of hypercholesterolemia and hypertriglyceridemia.

SOURCE – Bristol-Myers Squibb.

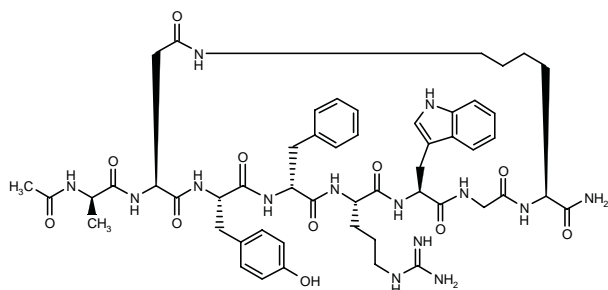
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1. Biller, S.A. et al. (Bristol-Myers Squibb Co.) *Conformationally restricted aromatic inhibitors of microsomal triglyceride transfer protein and method*. EP 0904262, JP 2000502355, WO 9726240.
2. Biller, S.A. et al. *Conformationally restricted aromatic inhibitors of microsomal triglyceride transfer protein and method*. US 5760246.
3. Gregg, R.E. and Wetterau, J.R. II (Bristol-Myers Squibb Co.) *MTP inhibitors and fat soluble vitamin therapeutic combinations to lower serum lipid levels*. WO 9850028.
4. Joshi, H.N. et al. *Polyethylene-glycol-polysorbate 80 solid dispersion to improve bioavailability of a water-insoluble drug*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3147.
5. Robl, J.A. et al. *A novel series of highly potent benzimidazole-based microsomal triglyceride transfer protein inhibitors*. J Med Chem 2001, 44(6): 851.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

295382

N-Acetyl-D-alanyl-L-aspartyl-L-tyrosyl-D-phenylalanyl-L-arginyl-L-tryptophyl-glycyl-L-lysineamide cyclic C-4.2-*N*-6.7-amide



C52 H68 N14 O11; Mol wt: 1065.1960

ACTION – A representative compound from a series of cyclic peptides with high affinity for melanocortin MC₄ and/or MC₃ receptor subtypes and selectivity relative to other melanocortin receptor subtypes, particularly MC₁ receptors. Potentially useful for the treatment of body weight disorders such as obesity, anorexia and cachexia, as well as depression, behavior-related disorders, memory-related disorders, cardiovascular disorders, inflammation, septic shock, cardiogenic shock, hypovolemic shock, sexual dysfunction, muscle atrophy and diseases associated with nerve growth and repair.

SOURCE – Procter & Gamble.

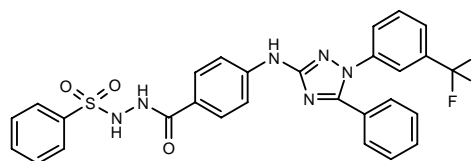
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295708

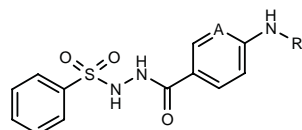
N'-[4-[5-Phenyl-1-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-3-ylamino]benzoyl]benzenesulfonylhydrazide

N'-(Phenylsulfonyl)-4-[5-phenyl-1-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-3-ylamino]benzohydrazide



C28 H21 F3 N6 O3 S; Mol wt: 578.5729

ACTION – Agent with high affinity for neuropeptide Y (NPY) receptors and low toxicity, potentially useful for the treatment of eating or metabolic disorders such as diabetes, obesity, bulimia and anorexia, as well as for the treatment of arterial hypertension, anxiety, depression, epilepsy, sexual dysfunction and sleep disorders. *In vitro*, compound exhibited an IC₅₀ value of 80 nM in a binding assay for NPY Y₅ receptors. *In vivo*, it was found to decrease food intake by 45% and body weight by 6.4% compared to baseline when given at 1 mg/kg i.p. to *ob/ob* mice. Other specifically claimed compounds from this series of aminotriazole derivatives are:



Compound	R1	A	Formula
295709	5-Ph-1,2,4-triazol-3-yl	CH	C ₂₁ H ₁₈ N ₆ O ₃ S
295710	5-Ph-1-(2-Pyr)-1,2,4-triazol-3-yl	CH	C ₂₆ H ₂₁ N ₇ O ₄ S
295711	5-oxo-1-(3-CF ₃ -Ph)-4,5-dihydro-1,2,4-triazol-3-yl	CH	C ₂₂ H ₁₇ F ₃ N ₆ O ₄ S
295713	5-oxo-1-(2-Pyr)-4,5-dihydro-1,2,4-triazol-3-yl	CH	C ₂₀ H ₁₇ N ₇ O ₄ S
295714	5-oxo-1-(2-Pyr)-4,5-dihydro-1,2,4-triazol-3-yl	N	C ₁₉ H ₁₆ N ₈ O ₄ S

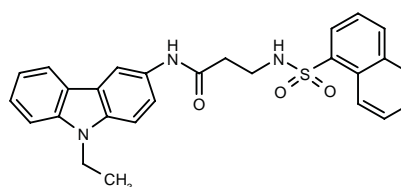
SOURCE – ADIR.

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1. Fauchere, J.-L. et al. (ADIR et Cie.) *Aminotriazole cpds., process for their preparation and pharmaceutical compsns. containing them*. EP 1044970, FR 2792314, JP 2000309579.

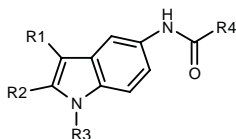
296185

N-(9-Ethyl-9*H*-carbazol-3-yl)-3-(1-naphthylsulfonylamido)-propionamide



C27 H25 N3 O3 S; Mol wt: 471.5785

ACTION – Agent with high affinity for neuropeptide Y (NPY) receptors, with potential in the treatment of eating or metabolic disorders such as obesity, bulimia, anorexia, diabetes, arteriosclerosis and hypercholesterolemia, as well as in the treatment of CNS disorders such as depression, epilepsy and dementia. *In vitro*, compound gave 100% inhibition of [³H]-NPY binding to human Y₅ receptors at 10 μM. In addition, it is reported to decrease food intake in *ob/ob* mice, as well as NPY-induced eating in mice following oral administration. Other exemplified compounds from this series of tricyclic derivatives include the following:



Compound	R1,R2	R3	R4	Formula
296186	-CH=CHCH=CH-	Et	cyclopropyl	C ₁₈ H ₁₈ N ₂ O
296187	-(CH ₂) ₄ -	i-Pr	NHCH ₂ CH ₂ OCH ₂ CH ₂ OH	C ₂₀ H ₂₉ N ₃ O ₃
296188	-(CH ₂) ₄ -	i-Pr	N(Me)CH ₂ CH ₂ OH	C ₁₉ H ₂₇ N ₃ O ₂
296189	-(CH ₂) ₄ -	i-Pr	2(S)-(HOCH ₂)- -1-pyrrolidinyl	C ₂₁ H ₂₉ N ₃ O ₂
296190	-(CH ₂) ₄ -	Pr	4-morpholinyl	C ₂₀ H ₂₇ N ₃ O ₂
296191	-(CH ₂) ₃ -	i-Pr	NH(CH ₂) ₄ OH	C ₁₉ H ₂₇ N ₃ O ₂

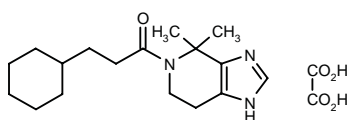
SOURCE – Meiji Seika.

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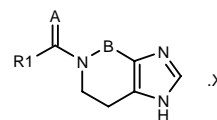
296381

3-Cyclohexyl-1-(4,4-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)propan-1-one oxalate



C₁₇ H₂₇ N₃ O . C₂ H₂ O₄; Mol wt: 379.4541

ACTION – Histamine H₃ receptor antagonist, potentially useful for the treatment of obesity and eating disorders, impaired glucose tolerance, type 2 diabetes, emesis, pain and neurogenic inflammation. Other exemplified compounds from this series of substituted imidazole derivatives include the following:



Compound	R1	A	B	X	Formula
296382	cyclopentyl-CH ₂ O	O	-CH ₂ -	oxalate	C ₁₃ H ₁₉ N ₃ O ₂ ·C ₂ H ₂ O ₄
296383	cyclohexyl- -CH ₂ CH ₂ O	O	-CH ₂ -	oxalate	C ₁₅ H ₂₃ N ₃ O ₂ ·C ₂ H ₂ O ₄
296384	4-Cl-PhCH ₂ NH	N(CN)	-CH ₂ -		C ₁₅ H ₁₅ ClN ₆
296385	4-Cl-Ph(CH ₂) ₃ NH	N(NO ₂)	-CH ₂ -		C ₁₆ H ₁₉ ClN ₆ O ₂
296386	4-t-Bu-Ph- CH ₂ CH ₂ NH	N(4-Me- PhSO ₂)	-CH ₂ -		C ₂₆ H ₃₃ N ₅ O ₂ S
296387	4-t-Bu-PhNH	O	-CH ₂ -		C ₁₇ H ₂₂ N ₄ O
296388	cyclohexyl-O	O	-(CH ₂) ₂ -		C ₁₄ H ₂₁ N ₃ O ₂
296389	NHCH ₂ CH ₂ Ph	O	-(CH ₂) ₂ -		C ₁₆ H ₂₀ N ₄ O
296390	trans-2-Ph- -cyclopropyl-NH	O	-(CH ₂) ₂ -		C ₁₇ H ₂₀ N ₄ O

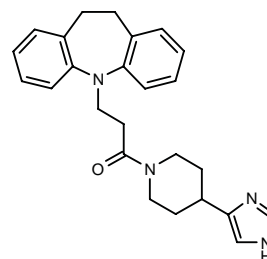
SOURCES – Boehringer Ingelheim; Novo Nordisk.

REFERENCES

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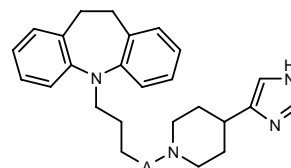
296554

3-(10,11-Dihydro-5H-dibenzo[*b,f*]azepin-5-yl)-1-[4-(1H-imidazol-4-yl)piperidin-1-yl]propan-1-one

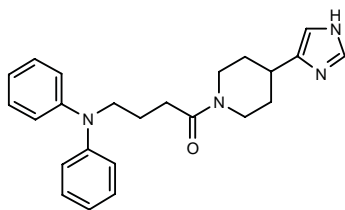


C₂₅ H₂₈ N₄ O; Mol wt: 400.5232

ACTION – Potent and selective histamine H₃ receptor antagonist, also reported to be able to interact with vanilloid receptors, 5-HT receptors and adrenoceptors. Potentially useful for the treatment or prevention of obesity and eating disorders, impaired glucose tolerance, type 2 diabetes, emesis, pain and neurogenic inflammation, as well as for inducing sleep. Other exemplified compounds from this series of piperidyl-imidazole derivatives are:



Compound	A	Formula
296555	bond	C ₂₆ H ₃₀ N ₄
296556	CO	C ₂₆ H ₃₀ N ₄ O
296558	CH ₂	C ₂₆ H ₃₂ N ₄



296557: C24 H28 N4 O

SOURCES – Boehringer Ingelheim; Novo Nordisk.

REFERENCES

1. Dörwald, F.Z. et al. (Novo Nordisk A/S;Boehringer Ingelheim GmbH) *Piperidyl-imidazole derivs., their preparation and therapeutic uses.* WO 0064884.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

CROFAB™

258496

Lyophilized preparation of ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep flocks immunized with one of the following North American snake venoms: Crotalus atrox, Crotalus adamanteus, Crotalus scutulatus and Agkistrodon piscivorus; to obtain the final antivenin product, the four different monospecific antivenins are mixed

Crotalidae polyvalent immune Fab (ovine)

ACTION – Antivenin consisting of specific antibody fragments that bind to toxic substances in the venom of most crotalids.

INDICATIONS – Treatment of North American crotalid snake envenomation.

PRESENTATION – Vials of a lyophilized preparation for i.v. administration after reconstitution containing up to 1.0 g of total protein and not less than the indicated number of mouse LD₅₀ neutralizing units: *C. atrox* (1350), *C. adamanteus* (800), *C. scutulatus* (5210) and *A. piscivorus* (460).

PROPRIETARY NAME – CroFab (US).

SOURCES – Protherics; marketed by Savage Laboratories (Altana).

REFERENCES

1. Consroe, P. et al. *Comparison of a new ovine antigen binding fragment (Fab) antivenin for United States Crotalidae with the commercial antivenin for protection against venom-induced lethality in mice.* Am J Trop Med Hyg 1995, 53(5): 507.
2. Dart, R.C. and McNally, J. *Efficacy, safety, and use of snake antivenoms in the United States.* Ann Emerg Med 2001, 37(2): 181.
3. Decker, W.W. et al. *Heat and motion stability of polyvalent Crotalidae antivenin, ovine Fab.* Toxicon 1998, 36(2): 377.
4. Hill, R.E. et al. *Time to reconstitution: Purified Fab antivenom vs. unpurified IgG antivenom.* Toxicon 2001, 39(5): 729.
5. *CroFab now available in the U.S. for treatment of poisonous snakebites.* DailyDrugNews.com (Daily Essentials) 2001, Feb 1.
6. *Protherics provides interim update on product development.* DailyDrugNews.com

(Daily Essentials) 2001, Jan 12.

7. *Protherics updates programs, announces collaboration with Lilly.* DailyDrugNews.com (Daily Essentials) 1999, Dec 23.

8. *Therapeutic Antibodies and Altana enter alliance for emergency medicine products.* DailyDrugNews.com (Daily Essentials) 1997, Oct 17.

9. *Therapeutic Antibodies announces results for the year ended December 31, 1996.* DailyDrugNews.com (Daily Essentials) 1997, March 27.

10. *Therapeutic Antibodies seeks FDA approval for antivenom product.* DailyDrugNews.com (Daily Essentials) 1998, May 12.

11. *Therapeutic Antibodies updates pipeline.* DailyDrugNews.com (Daily Essentials) 1998, Dec 7.

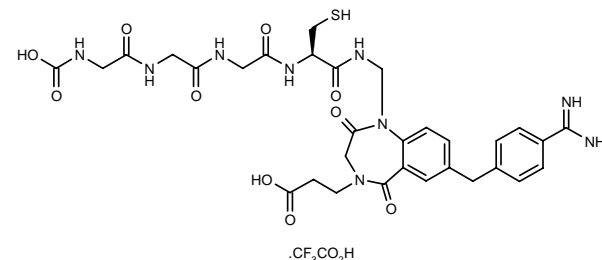
12. *Therapeutic Antibodies: Q3 1997 highlights.* DailyDrugNews.com (Daily Essentials) 1997, Dec 5.

13. *Therapeutic Antibodies: year-end 1998 highlights.* DailyDrugNews.com (Daily Essentials) 1999, April 27.

DIAGNOSTIC AGENTS

296008

3-[7-(4-Amidinobenzyl)-1-(N-carboxy-glycyl-glycyl-glycyl-L-cysteinamidomethyl)-2,5-dioxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-4-yl]propionic acid trifluoroacetate



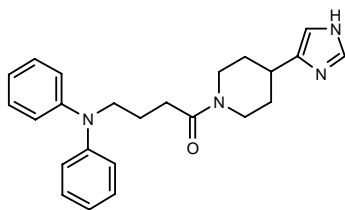
C31 H37 N9 O10 S . C2 H F3 O2; Mol wt: 841.7742

ACTION – A representative compound from a series comprising a gp11b/IIla receptor-binding benzodiazepine moiety covalently linked to a metal ion chelator, which may be labeled with a radionuclide such as ^{99m}Tc for imaging thrombi. The ^{99m}Tc derivative of this compound exhibited K_d values of 30.5 ± 6 and 13.5 ± 3 nM, respectively, for binding to resting and ADP-activated platelets and it exhibited good efficiency in imaging pulmonary emboli and deep vein thrombi in dogs following i.v. administration.

SOURCES – Diatide (Schering AG); Genentech.

REFERENCES

1. Dean, R.T. et al. (Diatide, Inc.;Genentech, Inc.) *Benzodiazepine derivs. for imaging thrombi.* WO 0061195.



296557: C24 H28 N4 O

SOURCES – Boehringer Ingelheim; Novo Nordisk.

REFERENCES

1. Dörwald, F.Z. et al. (Novo Nordisk A/S;Boehringer Ingelheim GmbH) *Piperidyl-imidazole derivs., their preparation and therapeutic uses.* WO 0064884.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

CROFAB™

258496

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11. *Therapeutic Antibodies updates pipeline.* DailyDrugNews.com (Daily Essentials) 1998, Dec 7.

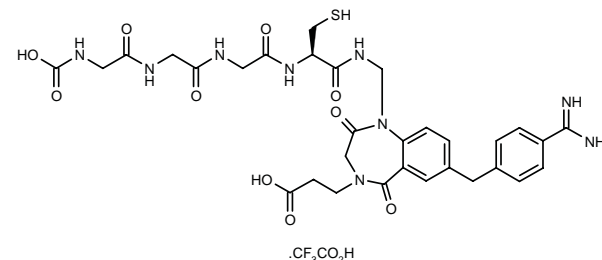
12. *Therapeutic Antibodies: Q3 1997 highlights.* DailyDrugNews.com (Daily Essentials) 1997, Dec 5.

13. *Therapeutic Antibodies: year-end 1998 highlights.* DailyDrugNews.com (Daily Essentials) 1999, April 27.

DIAGNOSTIC AGENTS

296008

3-[7-(4-Amidinobenzyl)-1-(N-carboxy-glycyl-glycyl-glycyl-L-cysteinamidomethyl)-2,5-dioxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-4-yl]propionic acid trifluoroacetate



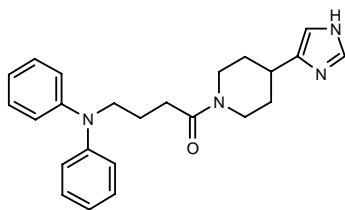
C31 H37 N9 O10 S . C2 H F3 O2; Mol wt: 841.7742

ACTION – A representative compound from a series comprising a gp11b/IIla receptor-binding benzodiazepine moiety covalently linked to a metal ion chelator, which may be labeled with a radionuclide such as ^{99m}Tc for imaging thrombi. The ^{99m}Tc derivative of this compound exhibited K_d values of 30.5 ± 6 and 13.5 ± 3 nM, respectively, for binding to resting and ADP-activated platelets and it exhibited good efficiency in imaging pulmonary emboli and deep vein thrombi in dogs following i.v. administration.

SOURCES – Diatide (Schering AG); Genentech.

REFERENCES

1. Dean, R.T. et al. (Diatide, Inc.;Genentech, Inc.) *Benzodiazepine derivs. for imaging thrombi.* WO 0061195.



296557: C24 H28 N4 O

SOURCES – Boehringer Ingelheim; Novo Nordisk.

REFERENCES

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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

CROFAB™

258496

Lyophilized preparation of ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep flocks immunized with one of the following North American snake venoms: Crotalus atrox, Crotalus adamanteus, Crotalus scutulatus and Agkistrodon piscivorus; to obtain the final antivenin product, the four different monospecific antivenins are mixed

Crotalidae polyvalent immune Fab (ovine)

ACTION – Antivenin consisting of specific antibody fragments that bind to toxic substances in the venom of most crotalids.

INDICATIONS – Treatment of North American crotalid snake envenomation.

PRESENTATION – Vials of a lyophilized preparation for i.v. administration after reconstitution containing up to 1.0 g of total protein and not less than the indicated number of mouse LD₅₀ neutralizing units: *C. atrox* (1350), *C. adamanteus* (800), *C. scutulatus* (5210) and *A. piscivorus* (460).

PROPRIETARY NAME – CroFab (US).

SOURCES – Protherics; marketed by Savage Laboratories (Altana).

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5. *CroFab now available in the U.S. for treatment of poisonous snakebites.* DailyDrugNews.com (Daily Essentials) 2001, Feb 1.
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9. *Therapeutic Antibodies announces results for the year ended December 31, 1996.* DailyDrugNews.com (Daily Essentials) 1997, March 27.

10. *Therapeutic Antibodies seeks FDA approval for antivenom product.* DailyDrugNews.com (Daily Essentials) 1998, May 12.

11. *Therapeutic Antibodies updates pipeline.* DailyDrugNews.com (Daily Essentials) 1998, Dec 7.

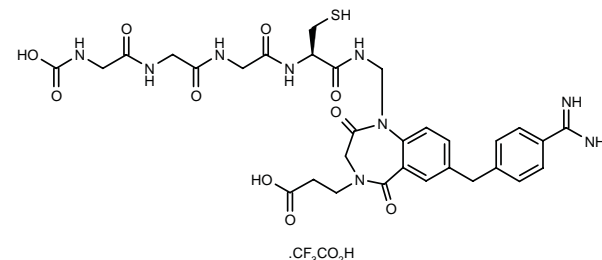
12. *Therapeutic Antibodies: Q3 1997 highlights.* DailyDrugNews.com (Daily Essentials) 1997, Dec 5.

13. *Therapeutic Antibodies: year-end 1998 highlights.* DailyDrugNews.com (Daily Essentials) 1999, April 27.

DIAGNOSTIC AGENTS

296008

3-[7-(4-Amidinobenzyl)-1-(N-carboxy-glycyl-glycyl-glycyl-L-cysteinamidomethyl)-2,5-dioxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-4-yl]propionic acid trifluoroacetate



C31 H37 N9 O10 S . C2 H F3 O2; Mol wt: 841.7742

ACTION – A representative compound from a series comprising a gp11b/IIla receptor-binding benzodiazepine moiety covalently linked to a metal ion chelator, which may be labeled with a radionuclide such as ^{99m}Tc for imaging thrombi. The ^{99m}Tc derivative of this compound exhibited K_d values of 30.5 ± 6 and 13.5 ± 3 nM, respectively, for binding to resting and ADP-activated platelets and it exhibited good efficiency in imaging pulmonary emboli and deep vein thrombi in dogs following i.v. administration.

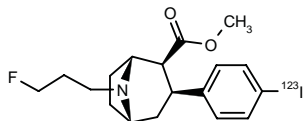
SOURCES – Diatide (Schering AG); Genentech.

REFERENCES

1. Dean, R.T. et al. (Diatide, Inc.;Genentech, Inc.) *Benzodiazepine derivs. for imaging thrombi.* WO 0061195.

IOFLUPANE (¹²³I)+

Prop INN

273559**(1*R*,2*S*,3*S*,5*S*)-8-(3-Fluoropropyl)-3-(4-[¹²³I]iodophenyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester**[¹²³I]-β-CIT-FP[¹²³I]-FP-CIT

C18 H23 F I N O2; Mol wt: 427.3827

ACTION – Iodine-labeled radiopharmaceutical imaging agent that binds to the dopamine transporter.

INDICATION – Detecting the loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndromes in order to help differentiate essential tremor from parkinsonian syndromes related to idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy.

PRESENTATION – Vials containing 185 MBq at reference time.**PROPRIETARY NAME** – DaTSCAN (EU).**SOURCE** – Nycomed Amersham.**REFERENCES**

1. Abi-Dargham, A. et al. *Human biodistribution and dosimetry of iodine-123-fluoroalkyl analogs of β-CIT*. Eur J Nucl Med 1997, 24(11): 1422.
2. Abi-Dargham, A. et al. *SPECT imaging of dopamine transporters in human brain with iodine-123-fluoroalkyl analogs of β-CIT*. J Nucl Med 1996, 37(7): 1129.
3. Baldwin, R.M. et al. *Regional brain uptake and pharmacokinetics of [¹²³I] N-ω-fluoroalkyl-2β-carboxy-3β-(4-iodophenyl)nortropane esters in baboons*. Nucl Med Biol 1995, 22(2): 211.
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6. Bergstrom, K.A. et al. *Characterization of C-11 or I-123 labelled β-CIT-FP and β-CIT-FE metabolism measured in monkey and human plasma. Identification of two labelled metabolites with HPLC*. Hum Psychopharmacol 1996, 11(6): 483.
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15. Lavalaye, J. et al. *[¹²³I]FP-CIT binding in rat brain after acute and sub-chronic administration of dopaminergic medication*. Eur J Nucl Med 2000, 27(3): 346.

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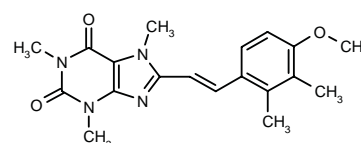
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*Drug Data Rep 2000, 022(05): 0478.

KF-21213**297488****8-[(*E*)-2-(2,3-Dimethyl-4-methoxyphenyl)vinyl]-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione**

C19 H22 N4 O3; Mol wt: 354.4078

ACTION – High-affinity adenosine A_{2A} receptor ligand (K_i = 3.0 nM) with > 3,300-fold selectivity over A₁ receptors. [¹¹C]-Labeled compound was studied as a selective ligand for mapping adenosine A_{2A} receptors in the CNS. Regional brain distribution studies in mice showed an increase in uptake of [¹¹C]-labeled compound in the striatum over the first 15 min after injection, followed by a gradual decrease, whereas uptake in the cortex and cerebellum rapidly decreased after injection. At 60 min after administration, the striatum:cortex and striatum:cerebellum uptake ratios were of 8.6 and 10.5, respectively. [¹¹C]-Labeled compound, used as a tracer for *ex vivo* autoradiography and PET in rats, clearly visualized striatal adenosine A_{2A} receptors.

SOURCE – Kyowa Hakko.

REFERENCES

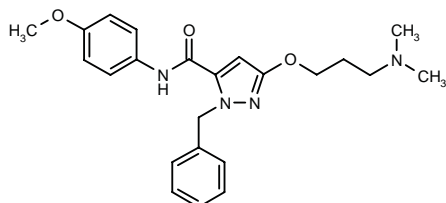
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3. Wang, W.F. et al. *Carbon-11-labeled KF21213: A highly selective ligand for mapping CNS adenosine A_{2A} receptors with positron emission tomography*. Nucl Med Biol 2000, 27(6): 541.

PHARMACOLOGICAL TOOLS

CFM-1571

297801

1-Benzyl-3-[3-(dimethylamino)propoxy]-N-(4-methoxyphenyl)-1H-pyrazole-5-carboxamide



C23 H28 N4 O3; Mol wt: 408.4992

ACTION – A selective activator of the nitric oxide receptor soluble guanylate cyclase (sGC; EC₅₀ = 5.49 μM) relative to other enzymes including phosphodiesterases and adenylate cyclase; it does not act as a nitric oxide (NO) donor. Compound inhibits collagen-induced human platelet aggregation with an IC₅₀ of 2.84 μM. Pharmacokinetic studies in male rats showed only moderate bioavailability after single oral doses of 5 mg/kg (12%), peak concentrations (6.4 ng/ml) being reached at 2.7 h postdose. Further optimization as regards pharmacokinetics and potency is in progress.

SOURCES – University College London, London (GB); Tripos.

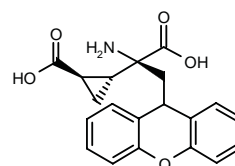
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2. Selwood, D.L. et al. *Synthesis and biological evaluation of novel pyrazoles and indazoles as activators of the nitric oxide receptor, soluble guanylate cyclase*. J Med Chem 2001, 44(1): 78.

LY-344545

294932

2(S)-Amino-2-[2(R)-carboxy-1(R)-cyclopropyl]-3-(9H-xanthen-9-yl)propionic acid



C20 H19 N O5; Mol wt: 353.3721

ACTION – Competitive metabotropic glutamate receptor antagonist with high affinity for the mglu₅ subtype (IC₅₀ = 5.5 μM) compared to mglu_{1α}, mglu₂, mglu₃, mglu₄, mglu₆, mglu₇ and mglu₈ subtypes (IC₅₀ = 39.5, 9.5, 10.7, > 100, 64.8, 45.0 and 62.0 μM, respectively), and little or no affinity for ionotropic glutamate receptors (IC₅₀ > 100 μM against NMDA, AMPA and kainate receptors). In functional studies, compound was found to antagonize glutamate-induced Ca²⁺ release in CHO cells transfected with rat mglu receptors, with selectivity for mglu_{5α} over mglu_{1α} subtypes (K_i = 2.1 and 20.5 μM, respectively). In addition, it antagonized (1S,3R)-ACPD-induced Ca²⁺ release in rat hippocampal slices (IC₅₀ = 6.8 μM) and (S)-3,5-DHPG-induced potentiation of NMDA depolarization in rat CA1 neurons (EC₅₀ = 10.6 μM). At higher concentrations (> 100 μM) compound exhibited NMDA-antagonist activity and blocked the induction, but not the expression, of long-term potentiation (LTP) at CA3 to CA1 synapses. Potentially useful as a pharmacological tool to elucidate the role of the mglu₅ receptor in physiological and pathological processes.

SOURCE – Lilly.

REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) *Excitatory amino acid receptor antagonists*. EP 0771196, JP 1998505597, US 5717109, WO 9607405.
2. Doherty, A.J. et al. *A novel, competitive mGlu5 receptor antagonist (LY344545) blocks DHPG-induced potentiation of NMDA responses but not the induction of LTP in rat hippocampal slices*. Br J Pharmacol 2000, 131(2): 239.
3. Ornstein, P.L. et al. *2-Substituted (2SR)-2-amino-2-(1SR, 2SR)-2-carboxycycloprop-1-ylglycines as potent and selective antagonists of group II metabotropic glutamate receptors. 2. Effects of aromatic substitution, pharmacological characterization, and bioavailability*. J Med Chem 1998, 41(3): 358.

ACTION – High-affinity adenosine A_{2A} receptor ligand (K_i = 3.0 nM) with > 3,300-fold selectivity over A₁ receptors. [¹¹C]-Labeled compound was studied as a selective ligand for mapping adenosine A_{2A} receptors in the CNS. Regional brain distribution studies in mice showed an increase in uptake of [¹¹C]-labeled compound in the striatum over the first 15 min after injection, followed by a gradual decrease, whereas uptake in the cortex and cerebellum rapidly decreased after injection. At 60 min after administration, the striatum:cortex and striatum:cerebellum uptake ratios were of 8.6 and 10.5, respectively. [¹¹C]-Labeled compound, used as a tracer for *ex vivo* autoradiography and PET in rats, clearly visualized striatal adenosine A_{2A} receptors.

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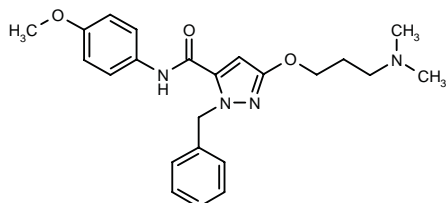
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PHARMACOLOGICAL TOOLS

CFM-1571

297801

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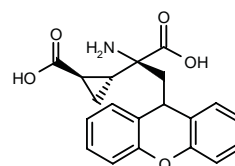
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LY-344545

294932

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SOURCE – Lilly.

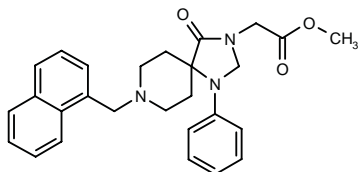
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NNC-63-0532

297995

2-[8-(1-Naphthylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester



C27 H29 N3 O3; Mol wt: 443.5441

ACTION – High-affinity nociceptin (ORL1) receptor (K_i = 7.3 nM) agonist with only moderate affinity for μ and κ opioid receptors (K_i = 140 and 405 nM, respectively) and dopamine D2S, D3 and D4.4 receptors (K_i = 209, 133 and 107 nM, respectively). Compound showed full agonist activity in *in vitro* functional assays in BHK cells expressing ORL1 receptors, with respective EC_{50} values of 109 and 305 nM for inhibition of forskolin-induced cAMP formation and stimulation of [35 S]GTP- γ S binding. It exhibited much weaker agonist activity at μ opioid receptors (EC_{50} > 50 μ M) and partial agonist activity at dopamine D2S receptors. Potentially useful as a pharmacological tool to elucidate the physiological role of ORL1 receptors.

SOURCE – Novo Nordisk.

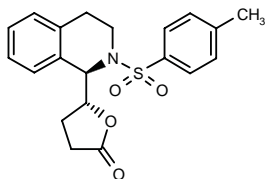
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2. Thomsen, C. and Hohlweg, R. (8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)-acetic acid methyl ester (NNC 63-0532) is a novel potent nociceptin receptor agonist. Br J Pharmacol 2000, 131(5): 903.

(+)-ROD-188^{1,3}

295366

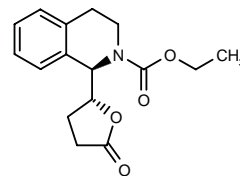
(+)-5-(R)-[2-(4-Methylphenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1(R)-yl]tetrahydrofuran-2-one



C20 H21 N O4 S; Mol wt: 371.4549

ACTION – Bicuculline derivative that acts as a positive allosteric modulator of GABA_A receptor activity, displaying neither agonist nor antagonist effects. Compound exhibited selective affinity for the rat $\alpha 6\beta 2\gamma 2$ subtype and binding studies demonstrated no binding to the GABA binding site and low affinity for the benzodiazepine site. (+)-ROD-188 was shown to stimulate currents induced by GABA in a concentration-dependent manner, apparently acting on a site different from that of GABA, pentobarbital, steroids, loreclezole or benzodiazepines. Studies in

cultures of rat hippocampal neurons indicated that it increased GABAergic neuronal transmission. Another related compound is:



ROD-185 [295364]:^{1,2} C16 H19 N O4

SOURCES – Universität Bern, Bern (CH); CNRS; Universität Wien, Vienna (AT).

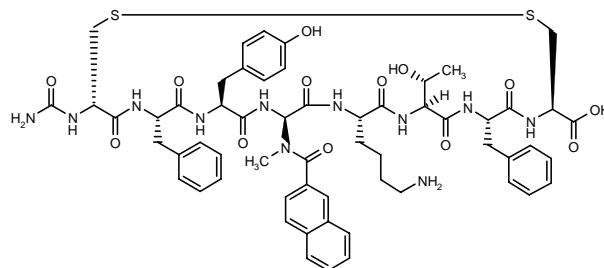
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SST₃-ODN-8

297097

N-Carbamoyl-D-cysteiny-L-phenylalanyl-L-tyrosyl-2(R)-[N-methyl-N-(2-naphthyl)carboxamido]glycyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteine cyclic (1-8)-disulfide



C58 H69 N11 O13 S2; Mol wt: 1192.3790

ACTION – Octapeptide somatostatin receptor antagonist with high affinity and selectivity for sst₃ receptors (IC_{50} = 6.7 nM). In *in vitro* assays using sst₃-transfected CCL39 cells, compound showed competitive antagonism of the somatostatin-28-induced inhibition of forskolin-stimulated cAMP production (pK_b = 9.07) and stimulation of phospholipase C activity (IC_{50} = 166 nM, pK_i = 9.2). Radioiodinated compound is reported to retain sst₃-antagonist activity and to be able to label sst₃-expressing cells and several human tumors, specifically inactive pituitary adenomas. Potentially useful as a tool for studying the physiological and pathophysiological role of sst₃ receptors, and also as a treatment for gastrointestinal and immune diseases.

SOURCES – Universität Bern, Bern (CH); Salk Institute for Biological Studies, La Jolla, CA (US).

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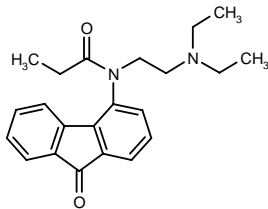
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ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

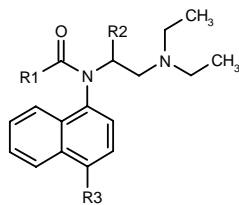
297465

N-[2-(Diethylamino)ethyl]-*N*-(9-oxo-9*H*-fluoren-4-yl)propionamide

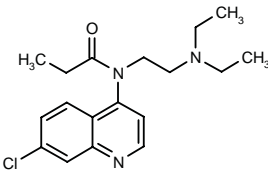


C22 H26 N2 O2; Mol wt: 350.4594

ACTION – Agent for the treatment of CNS disorders, particularly pain, depression, anxiety, schizophrenia, and neurodegenerative disorders such as Huntington’s disease, Alzheimer’s disease and amyotrophic lateral sclerosis. This compound is able to bind to the $\alpha 2\delta$ subunit of the calcium channel in brain tissue (IC_{50} = 0.058 μ M) and was active in reducing the hyperalgesic effects of carrageenan in the rat paw pressure test. Other exemplified compounds from this series of *N*-aryl-alkylamides are:



Compound	R1	R2	R3	Formula
297467	Et	H	Br	C ₁₉ H ₂₅ BrN ₂ O
297469	vinyl	H	Cl	C ₁₉ H ₂₃ ClN ₂ O
297470	Et	Me	NO ₂	C ₂₀ H ₂₇ N ₃ O ₃



297468: C18 H24 Cl N3 O

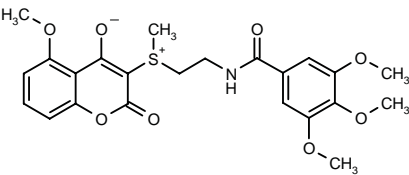
SOURCE – Pfizer.

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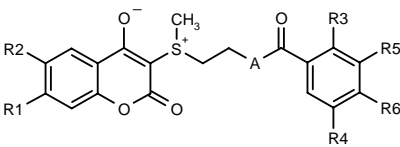
297579

5-Methoxy-3-[*S*-methyl-*S*-[2-(3,4,5-trimethoxybenzamido)ethyl]sulfonium]-2-oxo-2*H*-1-benzopyran-4-olate



C23 H25 N O8 S; Mol wt: 475.5155

ACTION – Analgesic agent active against substance P-induced pain in rats at 10 mg/kg p.o. A representative compound from a series of coumarin derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4=R5=R6	A	Formula
297580	OMe	H	H	OMe	NH	C ₂₃ H ₂₅ NO ₈ S
297581	Cl	H	OAc	H	O	C ₂₁ H ₁₇ ClO ₇ S
297582	H	OMe	OAc	H	O	C ₂₂ H ₂₀ O ₈ S
297583	H	H	H	OMe	N(Me)	C ₂₃ H ₂₅ NO ₇ S

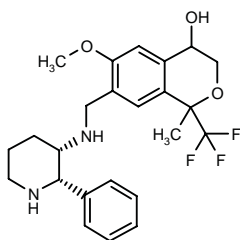
SOURCE – Otsuka.

REFERENCES

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297859

6-Methoxy-1-methyl-7-[2(*S*)-phenylpiperidin-3(*S*)-yl-aminomethyl]-1-(trifluoromethyl)-3,4-dihydro-1*H*-2-benzopyran-4-ol



C24 H29 F3 N2 O3; Mol wt: 450.4981

ACTION – Substance P antagonist, a specifically claimed compound from a series of 1-trifluoromethyl-4-hydroxy-7-piperidinylaminomethylchroman derivatives that are metabolites of previously reported substance P antagonists. Compound exhibited antiinflammatory activity in the capsaicin-induced plasma extravasation test in guinea pigs, producing 98% inhibition at 0.03 mg/kg p.o. Potentially useful for the treatment of emesis and acute or chronic pain.

SOURCE – Pfizer.

REFERENCES

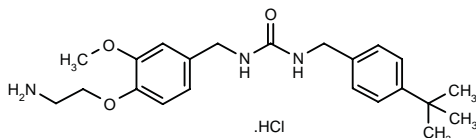
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SDZ-249-665*

250538

N-[4-(2-Aminoethoxy)-3-methoxybenzyl]-*N'*-(4-*tert*-butylbenzyl)urea hydrochloride

EC-665



C22 H31 N3 O3 . HCl; Mol wt: 421.9658

ACTION – Capsaicin analogue with comparable affinity to capsaicin for vanilloid receptors (IC_{50} = 760 nM vs. 850 nM for capsaicin) and 4-fold lower agonist activity (EC_{50} = 890 nM vs. 170 nM for stimulating Ca^{2+} uptake in rat dorsal root ganglion cells). Compound exhibited strong analgesic activity in a series of experiments in rats and mice including the mouse tail-flick assay (ED_{50} = 0.9 and 7 mg/kg s.c. and p.o., respectively), the acetic acid-induced writhing test in mice (ED_{50} = 0.4 and 4.5 mg/kg s.c. and p.o., respectively), the turpentine-induced rat paw hyperalgesia model (ED_{50} = 0.3 and 0.2 mg/kg s.c. and p.o., respectively) and the carrageenan-induced hyperalgesia model in guinea pig paw (ED_{50} = 3 mg/kg s.c.); in these tests compound was more active than capsaicin, morphine and nonsteroidal antiinflammatory drugs such as aspirin, indomethacin and paracetamol. In a model of urinary bladder inflammation in female rats, compound

was found to prevent both viscerovisceral hyperreflexia and viscerosomatic hyperalgesia. Unlike capsaicin, it did not produce unwanted side effects such as bronchoconstriction and blood pressure changes in the analgesic dose range, and it was not associated with nasal or ocular irritation. In addition, no sign of tolerance development was seen after 5 days' repeated treatment.

SOURCE – Novartis.

REFERENCES

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2. Jaggar, S.I. et al. The capsaicin analogue EC665 prevents the hyper-reflexia and referred mechanical hyperalgesia associated with inflammation of the rat urinary bladder. 9th World Congr Pain (Aug 22-27, Vienna) 1999, 22.

3. Jaggar, S.I. et al. The capsaicin analogue SDZ249-665 attenuates the hyper-reflexia and referred hyperalgesia associated with inflammation of the rat urinary bladder. Pain 2001, 89(2-3): 229.

4. James, I.F. et al. SDZ249-665: A non-excitatory capsaicin analogue with antihyperalgesic and antinociceptive properties. 9th World Congr Pain (Aug 22-27, Vienna) 1999, 22.

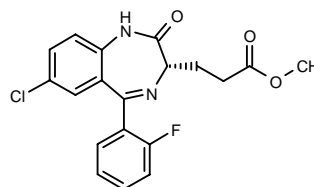
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*Identified compound **250538** Drug Data Rep 1997, 019(07): 0591.

ADJUNCTS TO ANESTHESIA

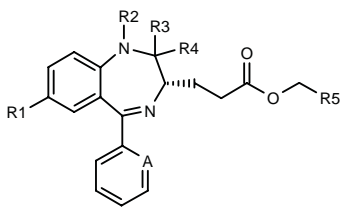
297743

3-[7-Chloro-5-(2-fluorophenyl)-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3(*S*)-yl]propionic acid methyl ester



C19 H16 Cl F N2 O3; Mol wt: 374.7974

ACTION – Sedative–hypnotic, anxiolytic, muscle relaxant and anticonvulsive agent, a representative compound from a series of short-acting benzodiazepines containing a carboxylic ester moiety, which are thereby capable of being inactivated by nonspecific tissue esterases in an organ-independent elimination mechanism, thereby providing a more predictable and reproducible pharmacodynamic profile. *In vitro*, compound exhibited a K_i value in the range of 1-50 nM against [3H]-flunitrazepam binding in rat, micropig and human brain cortex preparations. In addition, it produced a loss of righting reflex in rats at 10-100 mg/kg i.v. Compound is reported to be potentially useful for i.v. administration in the following clinical settings: preoperative sedation, anxiolysis and amnestic use for perioperative events; conscious sedation during short diagnostic, operative or endoscopic procedures; as a component for the induction and maintenance of general anesthesia, prior and/or concomitant to the administration of other anesthetic agents; ICU sedation. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
297744	Br	H	-O-		H	C(F)	C ₁₉ H ₁₆ BrFN ₂ O ₃
297745	Cl	H	-O-		Ph	C(F)	C ₂₅ H ₂₀ ClFN ₂ O ₃
297746	Cl	H	-O-		H	C(Cl)	C ₁₉ H ₁₆ Cl ₂ N ₂ O ₃
297747	Cl	Me	-O-		H	C(F)	C ₂₀ H ₁₈ ClFN ₂ O ₃
297748	Br	bond		NHMe	H	C(F)	C ₂₀ H ₁₉ BrFN ₃ O ₂
297749	Cl	-CH=CHN=			H	C(F)	C ₂₁ H ₁₇ ClFN ₃ O ₂
297750	Cl	-C(Me)=CHN=			H	C(F)	C ₂₂ H ₁₉ ClFN ₃ O ₂
297751	Cl	-CH=C(Me)N=			H	C(F)	C ₂₂ H ₁₉ ClFN ₃ O ₂
297752	Br	-C(Me)=CHN=			H	N	C ₂₁ H ₁₉ BrN ₄ O ₂
297753	Cl	-C(Me)=NN=			H	C(Cl)	C ₂₁ H ₁₈ Cl ₂ N ₄ O ₂
297754	Cl	-C(Me)=NN=			H	C(F)	C ₂₁ H ₁₈ ClFN ₄ O ₂
297755	Cl	-C(Me)=NCH=			H	C(F)	C ₂₂ H ₁₉ ClFN ₃ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

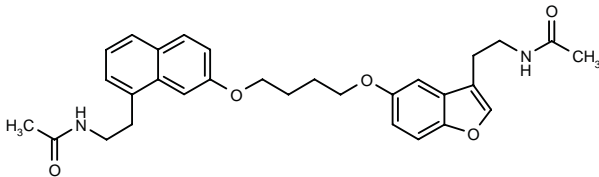
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

297236

N-[2-[7-[4-[3-(2-Acetamidoethyl)-1-benzofuran-5-yloxy]-butoxy]naphthalen-1-yl]ethyl]acetamide



C30 H34 N2 O5; Mol wt: 502.6076

ACTION – Agent with high affinity for melatonin receptors, potentially useful for the treatment of a broad range of disorders including seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exhibit anxiolytic activity and to have a potent effect on circadian rhythms via the melatonergic system in animal models, as well as to have low toxicity. A representative compound from a series of substituted dimeric carboxamide derivatives.

SOURCE – ADIR.

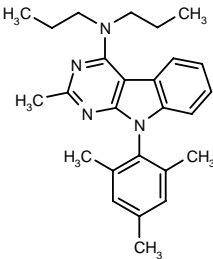
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ANXIOLYTICS

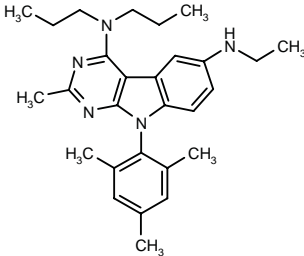
296719

N-[2-Methyl-9-(2,4,6-trimethylphenyl)-9H-pyrimido[4,5-b]-indol-4-yl]-N,N-dipropylamine



C26 H32 N4; Mol wt: 400.5668

ACTION – Selective corticotropin-releasing factor CRF₁ receptor antagonist with potential for the treatment of stress-related disorders, as well as anxiety, depression, headache, cardiovascular diseases, obesity and eating disorders. Another specifically claimed compound from this series of 9H-pyrimido[4,5-b]indole derivatives is:



296720: C28 H37 N5

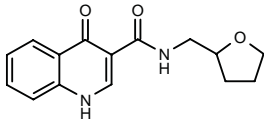
SOURCE – Neurogen.

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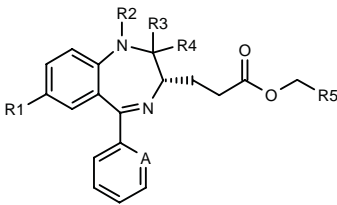
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297196

4-Oxo-N-(tetrahydrofuran-2-ylmethyl)-1,4-dihydroquinoline-3-carboxamide



C15 H16 N2 O3; Mol wt: 272.3024



Compound	R1	R2	R3	R4	R5	A	Formula
297744	Br	H	-O-	H	C(F)	C(F)	C ₁₉ H ₁₆ BrFN ₂ O ₃
297745	Cl	H	-O-	Ph	C(F)	C(F)	C ₂₅ H ₂₀ ClFN ₂ O ₃
297746	Cl	H	-O-	H	C(Cl)	C(Cl)	C ₁₉ H ₁₆ Cl ₂ N ₂ O ₃
297747	Cl	Me	-O-	H	C(F)	C(F)	C ₂₀ H ₁₈ ClFN ₂ O ₃
297748	Br	bond		NHMe	H	C(F)	C ₂₀ H ₁₉ BrFN ₃ O ₂
297749	Cl	-CH=CHN=			H	C(F)	C ₂₁ H ₁₇ ClFN ₃ O ₂
297750	Cl	-C(Me)=CHN=			H	C(F)	C ₂₂ H ₁₉ ClFN ₃ O ₂
297751	Cl	-CH=C(Me)N=			H	C(F)	C ₂₂ H ₁₉ ClFN ₃ O ₂
297752	Br	-C(Me)=CHN=			H	N	C ₂₁ H ₁₉ BrN ₄ O ₂
297753	Cl	-C(Me)=NN=			H	C(Cl)	C ₂₁ H ₁₈ Cl ₂ N ₄ O ₂
297754	Cl	-C(Me)=NN=			H	C(F)	C ₂₁ H ₁₈ ClFN ₄ O ₂
297755	Cl	-C(Me)=NCH=			H	C(F)	C ₂₂ H ₁₉ ClFN ₃ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

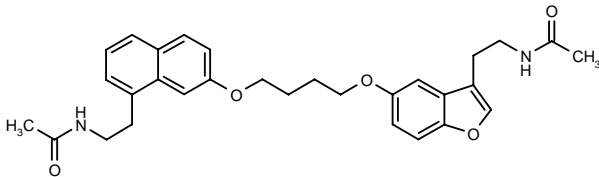
1. Feldman, P.L. et al. (Glaxo Group Ltd.) *Short-acting benzodiazepines*. WO 0069836.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

297236

N-[2-[7-[4-[3-(2-Acetamidoethyl)-1-benzofuran-5-yloxy]-butoxy]naphthalen-1-yl]ethyl]acetamide



C30 H34 N2 O5; Mol wt: 502.6076

ACTION – Agent with high affinity for melatonin receptors, potentially useful for the treatment of a broad range of disorders including seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exhibit anxiolytic activity and to have a potent effect on circadian rhythms via the melatonergic system in animal models, as well as to have low toxicity. A representative compound from a series of substituted dimeric carboxamide derivatives.

SOURCE – ADIR.

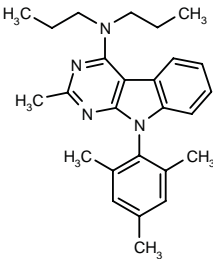
REFERENCES

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ANXIOLYTICS

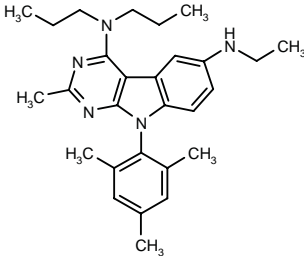
296719

N-[2-Methyl-9-(2,4,6-trimethylphenyl)-9H-pyrimido[4,5-b]-indol-4-yl]-N,N-dipropylamine



C26 H32 N4; Mol wt: 400.5668

ACTION – Selective corticotropin-releasing factor CRF₁ receptor antagonist with potential for the treatment of stress-related disorders, as well as anxiety, depression, headache, cardiovascular diseases, obesity and eating disorders. Another specifically claimed compound from this series of 9H-pyrimido[4,5-b]indole derivatives is:



296720: C28 H37 N5

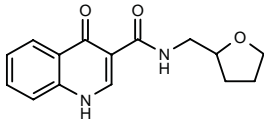
SOURCE – Neurogen.

REFERENCES

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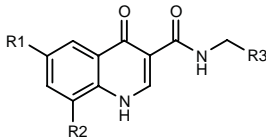
297196

4-Oxo-N-(tetrahydrofuran-2-ylmethyl)-1,4-dihydroquinoline-3-carboxamide



C15 H16 N2 O3; Mol wt: 272.3024

ACTION – Highly selective modulator of GABA_A brain receptors with potential in the treatment of anxiety, depression, overdose with benzodiazepines, Down’s syndrome, sleep and seizure disorders and for memory enhancement. Other compounds from this series of substituted 4-oxo-quinoline-3-carboxamides include the following:



Compound	R1	R2	R3	Formula
297197	H	H	i-Bu	C ₁₅ H ₁₈ N ₂ O ₂
297198	H	H	3-F-Ph	C ₁₇ H ₁₃ FN ₂ O ₂
297199	Cl	H	4-(EtNHCH2)-Ph	C ₂₀ H ₂₀ ClN ₃ O ₂
297200	CH2OMe	H	2-thienyl	C ₁₇ H ₁₆ N ₂ O ₃ S
297201	4-morpholinyl	H	Pr	C ₁₈ H ₂₃ N ₃ O ₃
297202	OEt	H	3-Pyr	C ₁₈ H ₁₇ N ₃ O ₃
297203	OEt	H	4-(1-imidazolyl-CH2)-Ph	C ₂₃ H ₂₂ N ₄ O ₃
297204	H	F	Ph	C ₁₇ H ₁₃ FN ₂ O ₂
297205	OEt	H	4-(4-morpholinyl-CH2CH2OCH2)-Ph	C ₂₆ H ₃₁ N ₃ O ₅
297206	OEt	H	3-[4-(3-CF3-Ph)-1-Piz-CH2]-Ph	C ₃₁ H ₃₁ F ₃ N ₄ O ₃

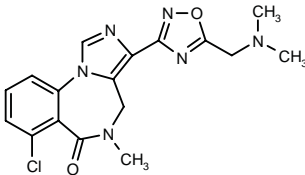
SOURCE – Neurogen.

REFERENCES

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297788

7-Chloro-3-[5-(dimethylaminomethyl)-1,2,4-oxadiazol-3-yl]-5-methyl-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one



C17 H17 Cl N6 O2; Mol wt: 372.8143

ACTION – Agent for the treatment of anxiety disorders, insomnia, mood disorders, psychotic disorders and convulsive disorders that exhibits high affinity *in vitro* for benzodiazepine receptors (pK_i = 9.1 against [³H]-flumazenil binding in homogenized rat cortex preparations), as well as potent anxiolytic activity in the mouse operant conflict model (MED = 3 mg/kg p.o.), with a rapid onset of action. Compound exhibits substantially fewer adverse effects characteristic of conventional benzodiazepine anxiolytics; in particular, it showed reduced liability for motor impairment (ED₅₀ > 10 mg/kg i.v. in the rotarod test in mice), low ethanol interaction in mice, minimal withdrawal signs in chronically treated mice subsequently challenged with a benzodiazepine receptor antagonist such as sarmazenil, minimal reduction (i.e., tolerance) of the anxiolytic effect in mice after chronic treatment and

minimal cognitive impairment in rats, and it produced minimal or no inhibition of cytochrome P-450 enzymes.

SOURCE – Roche.

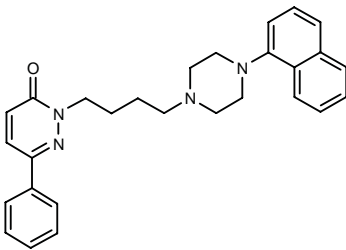
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ANTIPSYCHOTIC DRUGS

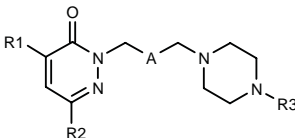
297307

2-[4-[4-(1-Naphthalenyl)piperazin-1-yl]butyl]-6-phenylpyridazin-3(2*H*)-one



C28 H30 N4 O; Mol wt: 438.5720

ACTION – Antipsychotic agent, a combined 5-HT_{1A}, 5-HT₂ and dopamine D2 receptor agonist reported to exhibit nanomolar affinity for these three receptors in binding assays. Other specifically claimed compounds from this series of arylpiperazinyalkyl-3(2*H*)-pyridazinones include the following:



Compound	R1	R2	R3	A	Formula
297308	H	Me	1-Naph	-CH2-	C ₂₂ H ₂₆ N ₄ O
297309	H	Ph	3-Cl-Ph	-CH2-	C ₂₃ H ₂₅ ClN ₄ O
297310	H	Ph	3-CF3-Ph	-(CH2)2-	C ₂₅ H ₂₇ F ₃ N ₄ O
297311	H	Me	2-MeO-Ph	-(CH2)2-	C ₂₀ H ₂₆ N ₄ O ₂
297312	H	Me	3-Cl-Ph	-CH2-	C ₁₈ H ₂₃ ClN ₄ O
297313	H	Me	3-CF3-Ph	bond	C ₁₈ H ₂₁ F ₃ N ₄ O
297314	Me	Ph	3-CF3-Ph	-(CH2)2-	C ₂₆ H ₂₉ F ₃ N ₄ O

SOURCE – FAES.

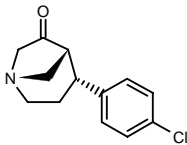
REFERENCES

1. Orjales Venero, A. and Garcia-Dominguez, N. (FAES SA) *Arylpiperazinyalkyl-3(2H)-pyridazinones as serotonin 5HT and dopamine D2 receptor agonists*. EP 1057820, JP 2001002659.

TREATMENT OF MOOD
DISORDERS

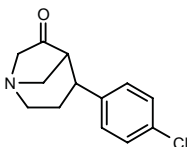
296872

(-)-endo-4-(4-Chlorophenyl)-1-azabicyclo[3.2.1]octan-6-one



C13 H14 Cl N O; Mol wt: 235.7126

ACTION – 5-HT reuptake inhibitor with potential in the treatment of depression, obsessive–compulsive disorder, panic disorders, memory deficits, obesity, anxiety, alcoholism and eating disorders. *In vitro*, compound inhibited 5-HT, dopamine and norepinephrine uptake with K_i values of 1890 ± 440 , $16,500 \pm 970$ and $70,900 \pm 18,000$ nM, respectively. Other specifically claimed compounds from this series of bi- and tricyclic aza compounds are:



Compound	Isomer	Formula
296873	(±)-endo	C ₁₃ H ₁₄ ClNO
296874	(+)-endo	C ₁₃ H ₁₄ ClNO
296875	(±)-exo	C ₁₃ H ₁₄ ClNO
296876	(-)-exo	C ₁₃ H ₁₄ ClNO
296877	(+)-exo	C ₁₃ H ₁₄ ClNO

SOURCE – Georgetown University, Washington, DC (US).

REFERENCES

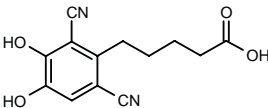
1. Kozikowski, A.P. and Smith, M.P. (Georgetown University) *Bi- and tri-cyclic aza cpds. and their uses.* US 6150376.

NEUROLOGIC DRUGS

TREATMENT OF EXTRAPYRAMIDAL
MOVEMENT DISORDERS

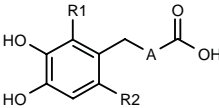
296862

5-(2,6-Dicyano-3,4-dihydroxyphenyl)pentanoic acid



C13 H12 N2 O4; Mol wt: 260.2478

ACTION – Potent and long-acting catechol *O*-methyl-transferase (COMT) inhibitor ($IC_{50} = 15$ nM), potentially useful for the treatment of Parkinson’s disease and hypertension. Plasma concentrations of 2000 and 150 ng/ml were determined 30 min and 5 h, respectively, after 10 mg/kg p.o. in rats. Other exemplified catechol derivatives include the following:



Compound	R1=R2	A	Formula
296863	NO2	-CH2-	C ₉ H ₈ N ₂ O ₈
296864	NO2	-(CH2)3-	C ₁₁ H ₁₂ N ₂ O ₈
296865	CHO	-(CH2)3-	C ₁₃ H ₁₄ O ₆
296866	CHO	-CH2-	C ₁₁ H ₁₀ O ₆
296867	CN	-CH2-	C ₁₁ H ₈ N ₂ O ₄

SOURCE – Orion Corporation.

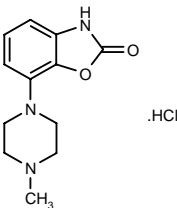
REFERENCES

1. Pystynen, J. et al. (Orion Corporation) *Catechol derivs.* US 6150412, WO 9637456.

SLV-308*

290288

7-(4-Methyl-1-piperazinyl)benzoxazol-2(3*H*)-one mono-hydrochloride

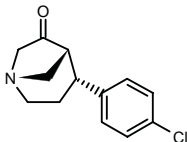


C12 H15 N3 O2 . HCl; Mol wt: 269.7304

TREATMENT OF MOOD
DISORDERS

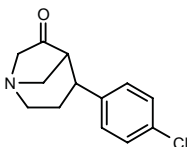
296872

(-)-endo-4-(4-Chlorophenyl)-1-azabicyclo[3.2.1]octan-6-one



C13 H14 Cl N O; Mol wt: 235.7126

ACTION – 5-HT reuptake inhibitor with potential in the treatment of depression, obsessive–compulsive disorder, panic disorders, memory deficits, obesity, anxiety, alcoholism and eating disorders. *In vitro*, compound inhibited 5-HT, dopamine and norepinephrine uptake with K_i values of 1890 ± 440 , $16,500 \pm 970$ and $70,900 \pm 18,000$ nM, respectively. Other specifically claimed compounds from this series of bi- and tricyclic aza compounds are:



Compound	Isomer	Formula
296873	(±)-endo	C ₁₃ H ₁₄ ClNO
296874	(+)-endo	C ₁₃ H ₁₄ ClNO
296875	(±)-exo	C ₁₃ H ₁₄ ClNO
296876	(-)-exo	C ₁₃ H ₁₄ ClNO
296877	(+)-exo	C ₁₃ H ₁₄ ClNO

SOURCE – Georgetown University, Washington, DC (US).

REFERENCES

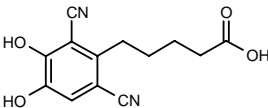
1. Kozikowski, A.P. and Smith, M.P. (Georgetown University) *Bi- and tri-cyclic aza cpds. and their uses.* US 6150376.

NEUROLOGIC DRUGS

TREATMENT OF EXTRAPYRAMIDAL
MOVEMENT DISORDERS

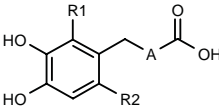
296862

5-(2,6-Dicyano-3,4-dihydroxyphenyl)pentanoic acid



C13 H12 N2 O4; Mol wt: 260.2478

ACTION – Potent and long-acting catechol *O*-methyl-transferase (COMT) inhibitor ($IC_{50} = 15$ nM), potentially useful for the treatment of Parkinson’s disease and hypertension. Plasma concentrations of 2000 and 150 ng/ml were determined 30 min and 5 h, respectively, after 10 mg/kg p.o. in rats. Other exemplified catechol derivatives include the following:



Compound	R1=R2	A	Formula
296863	NO2	-CH2-	C ₉ H ₈ N ₂ O ₈
296864	NO2	-(CH2)3-	C ₁₁ H ₁₂ N ₂ O ₈
296865	CHO	-(CH2)3-	C ₁₃ H ₁₄ O ₆
296866	CHO	-CH2-	C ₁₁ H ₁₀ O ₆
296867	CN	-CH2-	C ₁₁ H ₈ N ₂ O ₄

SOURCE – Orion Corporation.

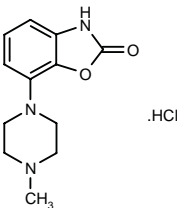
REFERENCES

1. Pystynen, J. et al. (Orion Corporation) *Catechol derivs.* US 6150412, WO 9637456.

SLV-308*

290288

7-(4-Methyl-1-piperazinyl)benzoxazol-2(3*H*)-one mono-hydrochloride



C12 H15 N3 O2 . HCl; Mol wt: 269.7304

ACTION – Antiparkinsonian agent, a high-affinity ligand for dopamine D2 receptors ($pK_i = 7.5$) with partial agonist activity at D2 receptors ($pEC_{50} = 7.5$ for attenuation of forskolin-induced cAMP accumulation in CHO cells stably transfected with human D2 receptors) and weaker but full agonist activity at 5-HT_{1A} receptors ($pEC_{50} = 6.3$). as well as α_1 -adrenoceptor-agonist activity *in vivo*. Microdialysis experiments in nucleus accumbens in rats treated with compound showed a reduction in extracellular dopamine content ($ED_{75} = 0.4$ mg/kg p.o.), but no significant effect on extracellular 5-HT levels. Compound was found to reduce spontaneous locomotor activity in an open-field test in rats with ED_{50} values of 0.02 mg/kg i.p. and 0.03 mg/kg p.o., and to induce contralateral turning behavior in unilaterally 6-OHDA-lesioned rats, with a minimum effective dose of 0.03 mg/kg p.o. In an animal model of Parkinson's disease in MPTP-treated marmosets, it induced marked and long-lasting antiparkinsonian effects at doses of 0.1 mg/kg i.p. and above. Moreover, an antidepressant effect was seen in the forced swimming test in rats ($ED_{50} = 0.03$ -0.2 mg/kg i.p. for reduction in immobility time) and anxiolytic-like activity in the ultrasonic vocalization test in both rat pups ($ED_{50} = 0.1$ mg/kg i.p.) and adult rats ($ED_{50} = 0.006$ mg/kg p.o.). Compound showed 60-80% oral bioavailability in rats and cynomolgus monkeys and a half-life of 2-8 h in rats and 5-12 h in monkeys. Toxicology testing in rats and monkeys indicated a large therapeutic index, and preliminary studies in healthy volunteers have shown good tolerance following multiple doses of up to 1 mg t.i.d.

SOURCE – Solvay.

REFERENCES

1. Toorop, G.P. et al. (Duphar International Research BV) *New piperazine and piperidine cpds.* WO 0029397.
2. Johnston, L.C. et al. *The novel dopamine D2 partial agonist, SLV308, reverses motor disability in MPTP-lesioned common marmosets (Callithrix jacchus).* Br J Pharmacol 2001, 133(Suppl.): Abstr 134P.

3. *Solvay strategies - pharmaceuticals.* Solvay Product Pipeline 1999, April 29.

MONOGRAPH – Feenstra, R. et al. SLV308. Drugs Fut 2001, 26(2): 0128.

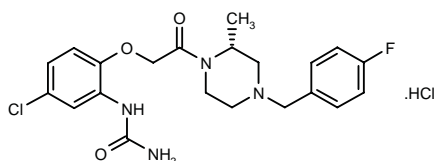
*Identified compound **290288** (see **290287**) Drug Data Rep 2000, 022(09): 0776.

THERAPY OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

BX-471

300274

N-[5-Chloro-2-[2-[4-(4-fluorobenzyl)-2(*R*)-methylpiperazin-1-yl]-2-oxoethoxy]phenyl]urea hydrochloride



C21 H24 Cl F N4 O3 . HCl; Mol wt: 471.3575

ACTION – Potent, selective and orally active chemokine CCR1 receptor antagonist proven to displace the binding of the CCR1 ligands macrophage inflammatory protein-1 α (MIP-1 α), RANTES and monocyte chemoattractant protein-3 (MCP-3) to CCR1-transfected HEK293 cells with respective K_i values of 5.5, 2.8 and 1.0 nM; it exhibited > 10,000-fold selectivity for CCR1 versus all other G-protein-coupled receptors and showed functional antagonism at CCR1 receptors, as demonstrated *in vitro* in CCR1-expressing HEK293 cells, where it inhibited agonist-induced Ca^{2+} mobilization ($IC_{50} = 5, 2$ and 6 nM, respectively, against MIP-1 α , RANTES and MCP-3). Pharmacokinetic studies demonstrated that compound is orally available (60% in dogs) and relatively stable in plasma. *In vivo*, it was active in an experimental allergic encephalomyelitis (EAE) model of multiple sclerosis in rats, where doses of 5, 20 and 50 mg/kg dose-dependently decreased the severity of the disease, as well as in a rat heart transplant rejection model, where, combined with subtherapeutic doses of ciclosporin, it prolonged the time to transplant rejection in comparison with ciclosporin alone. The *in vivo* activity of compound appeared to correlate well with inhibition of chemotaxis in human lymphocytes and monocytes induced by MIP-1 α and RANTES, as well as of the adhesion of activated immune cells to inflamed endothelium. Potentially useful for the treatment of autoimmune or inflammatory disease, as well as for the prevention of transplant rejection.

SOURCE – Berlex.

REFERENCES

1. Bauman, J.G. et al. (Schering AG) *Piperazine derivs. and their use as anti-inflammatory agents.* US 6207665, WO 9856771.
2. Hesselgesser, J. and Horuk, R. *The CCR1 antagonist BX 471 is effective in animal models of multiple sclerosis and organ transplant rejection.* Chemokines Chemokine Receptors (Feb 16-21, Taos) 2001, Abstr.
3. Horuk, R. et al. *A non-peptide functional antagonist of the CCR1 chemokine receptor is effective in rat heart transplant rejection.* J Biol Chem 2001, 276(6): 4199.
4. Liang, M. et al. *Identification and characterization of a potent, selective, and orally active antagonist of the CC chemokine receptor-1.* J Biol Chem 2000, 275(25): 19000.

MAB F28C4

297534

Idiotypic antibody directed against amino acids 1-9 of myelin basic protein

ACTION – Idiotypic antibody directed against myelin basic protein, potentially useful for the treatment of demyelinating autoimmune conditions such as allergic encephalomyelitis and multiple sclerosis. F28C4 demonstrated protective effects in several models of experimental allergic encephalomyelitis.

SOURCE – UAB Research Foundation, Birmingham, AL (US).

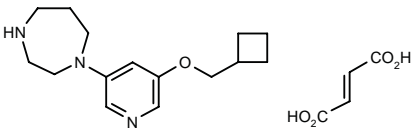
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1. Blalock, J.E. et al. (UAB Research Foundation) *Antibody vaccine for autoimmune diseases.* WO 0069461.

TREATMENT OF
DISORDERS OF COGNITION

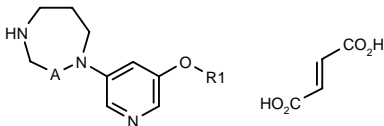
296619

1-[5-(Cyclobutylmethoxy)pyridin-3-yl]perhydro-1,4-diazepine fumarate



C15 H23 N3 O . C4 H4 O4; Mol wt: 377.4383

ACTION – Nicotinic acetylcholine receptor (nAChR) ligand with potential for the treatment of conditions involving the cholinergic system of the CNS including Alzheimer’s disease and other cognitive and neurodegenerative disorders, disorders associated with smooth muscle contraction, endocrine disorders, pain, inflammatory disorders and withdrawal from tobacco and other addictive substances. Compound gave IC₅₀ values against [³H]-cytisine (α4β2 subunit) binding in rat cortical preparations, [³H]-epibatidine (α4β2 subunit) binding in rat forebrain preparations and [³H]-α-bungarotoxin (α7 and α1 subunits) binding in rat cortical preparations of 0.001, 0.004 and > 30 μM, respectively. Other compounds from this series of heteroaryl diazacycloalkanes include the following:



Compound	R1	A	Formula
296624	Bu	-(CH2)2-	C ₁₅ H ₂₈ N ₃ O.C ₄ H ₄ O ₄
296626	CH2CH=CHPr	-CH2-	C ₁₆ H ₂₈ N ₃ O.C ₄ H ₄ O ₄
296628	CH=C(Me)2	-CH2-	C ₁₄ H ₂₁ N ₃ O.C ₄ H ₄ O ₄

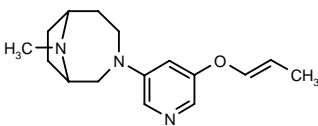
SOURCE – NeuroSearch.

REFERENCES

1. Nielsen, S.F. et al. (NeuroSearch A/S) *Heteroaryl diazacycloalkanes, their preparation and use*. WO 0064885.

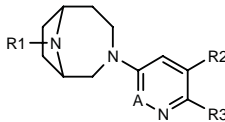
296735

9-Methyl-3-[5-[1(*E*)-propenyloxy]pyridin-3-yl]-3,9-diazabicyclo[4.2.1]nonane

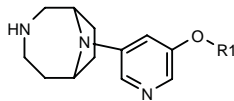


C16 H23 N3 O; Mol wt: 273.3777

ACTION – Nicotinic acetylcholine receptor (nAChR) modulator with selectivity for the nAChR α4β2 subtype, as demonstrated in binding assays by IC₅₀ values of 0.005, 0.016 and 10.0 μM, respectively, against [³H]-cytisine (α4β2 subunit) binding in rat cortical preparations, [³H]-epibatidine (α4β2 subunit) binding in rat forebrain preparations and [³H]-α-bungarotoxin (α7 and α1 subunits) binding in rat cortical preparations. Potentially useful for the treatment of conditions involving the cholinergic system of the CNS including Alzheimer’s disease and other cognitive and neurodegenerative disorders, as well as disorders associated with smooth muscle contraction, endocrine disorders, pain, inflammatory disorders and withdrawal from tobacco and other addictive substances. Other exemplified compounds from this series of heteroaryl diazabicycloalkanes include the following:



Compound	R1	R2	R3	A	Formula
296736	Me	H	Cl	N	C ₁₂ H ₁₇ ClN ₄
296737	H	H	Cl	N	C ₁₁ H ₁₅ ClN ₄
296738	H	OCH=CHMe	H	CH	C ₁₅ H ₂₁ N ₃ O
296739	H	vinyl-O	H	CH	C ₁₄ H ₁₉ N ₃ O
296740	H	OEt	H	CH	C ₁₄ H ₂₁ N ₃ O
296741	Me	OEt	H	CH	C ₁₅ H ₂₃ N ₃ O
296742	Me	vinyl-O	H	CH	C ₁₅ H ₂₁ N ₃ O



Compound	R1	Formula
296743	Et	C ₁₄ H ₂₁ N ₃ O
296744	CH=CHMe	C ₁₅ H ₂₁ N ₃ O
296745	Me	C ₁₃ H ₁₉ N ₃ O

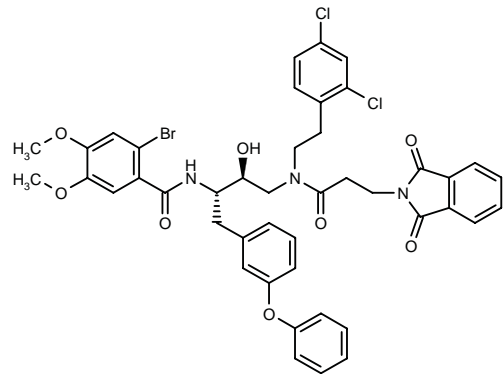
SOURCE – NeuroSearch.

REFERENCES

1. Peters, D. et al. (NeuroSearch A/S) *Heteroaryl diazabicycloalkanes, their preparation and use*. WO 0066586.

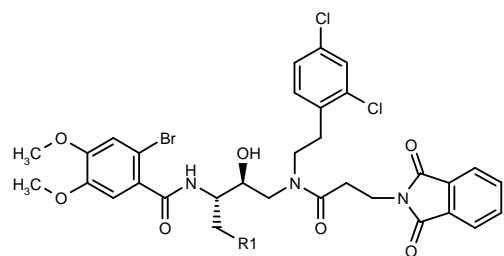
296858

2-Bromo-*N*-[3-[*N*-(2,4-dichlorophenyl)ethyl]-3-(1,3-dioxo-2,3-dihydro-1 *H*-isoindol-2-yl)propionamido]-2(*S*)-hydroxy-1(*S*)-(3-phenoxybenzyl)propyl]-4,5-dimethoxybenzamide



C44 H40 Br Cl2 N3 O8; Mol wt: 889.6230

ACTION – Nonpeptide inhibitor of cathepsin D ($K_i = 1.9 \pm 0.2$ nM), expected to be useful for the treatment of cancer, particularly breast cancer, and Alzheimer’s disease. Other exemplified compounds are:



Compound	R1	Formula
296859	2-Naph	C ₄₂ H ₃₈ BrCl ₂ N ₃ O ₇
296860	4-Ph-Ph	C ₄₄ H ₄₀ BrCl ₂ N ₃ O ₇
296861	4-Br-Ph	C ₃₈ H ₃₅ Br ₂ Cl ₂ N ₃ O ₇

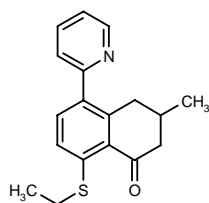
SOURCE – University of California, Oakland, Oakland, CA (US).

REFERENCES

1. Kick, E.K. et al. (University of California, Oakland) *Nanomolar, non-peptide inhibitors of cathepsin D*. US 6150416.

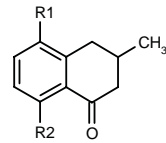
297241

8-(Ethylsulfanyl)-3-methyl-5-(2-pyridinyl)-1,2,3,4-tetrahydronaphthalen-1-one



C18 H19 N O S; Mol wt: 297.4201

ACTION – Agent for enhancing cognition, particularly for the treatment of Alzheimer’s disease, with selective affinity for human GABA_A α5 receptors. A representative compound from a series of substituted tetralone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
297242	5-pyrimidinyl	SEt	C ₁₇ H ₁₈ N ₂ OS
297243	2-pyrazinyl	SEt	C ₁₇ H ₁₈ N ₂ OS
297245	2-thiazolyl	1-Me-1,2,4-triazol-3-yl-CH2S	C ₁₈ H ₁₈ N ₄ OS ₂
297246	1-oxido-2-Pyr	2-thienyl-S	C ₂₀ H ₁₇ NO ₂ S ₂
297247	2-thiazolyl	OSO2CF3	C ₁₅ H ₁₂ F ₃ NO ₄ S ₂
297248	2-thiazolyl	2-thienyl-SO2O	C ₁₈ H ₁₅ NO ₄ S ₃

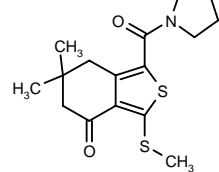
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Bryant, H.J. et al. (Merck Sharp & Dohme Ltd.) *Substd. tetralone derivs. for enhancing cognition*. US 6156761.

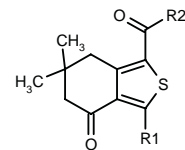
297250

6,6-Dimethyl-3-(methylsulfanyl)-1-(1-pyrrolidinylcarbonyl)-4,5,6,7-tetrahydrobenzo[*c*]thien-4-one



C16 H21 N O2 S2; Mol wt: 323.4789

ACTION – Agent for enhancing cognition, particularly for the treatment of Alzheimer’s disease, with selective affinity for human GABA_A α5 receptors. A representative compound from a series of substituted thienylcyclohexanone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
297251	SMe	N(Me)2	C ₁₄ H ₁₉ NO ₂ S ₂
297252	SMe	cyclohexyl-N(Me)	C ₁₉ H ₂₇ NO ₂ S ₂
297253	SPh	1-pyrrolidinyl	C ₂₁ H ₂₃ NO ₂ S ₂
297254	SEt	1-pyrrolidinyl	C ₁₇ H ₂₃ NO ₂ S ₂
297255	2-thiazolyl-S	1-pyrrolidinyl	C ₁₈ H ₂₀ N ₂ O ₂ S ₃
297256	SMe	hexahydro-1-azepinyl	C ₁₈ H ₂₅ NO ₂ S ₂
297257	SCH2CF3	1-pyrrolidinyl	C ₁₇ H ₂₀ F ₃ NO ₂ S ₂
297258	i-PrS	1-pyrrolidinyl	C ₁₈ H ₂₅ NO ₂ S ₂
297259	OPh	1-pyrrolidinyl	C ₂₁ H ₂₃ NO ₃ S
297260	SMe	4-morpholinyl	C ₁₈ H ₂₁ NO ₃ S ₂
297261	SMe	4-Me-1-Piz	C ₁₇ H ₂₄ N ₂ O ₂ S ₂

SOURCE – Merck Sharp & Dohme.

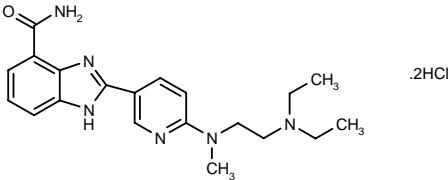
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1. Broughton, H.B. and Chambers, M.S. (Merck Sharp & Dohme Ltd.) *Substd. thienylcyclohexanone derivs. for enhancing cognition*. US 6156787.

TREATMENT OF CEREBROVASCULAR DISEASES

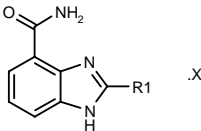
297069

2-[6-[N-[2-(Diethylamino)ethyl]-N-methylamino]pyridin-3-yl]-1H-benzimidazole-4-carboxamide dihydrochloride



C20 H26 N6 O . 2HCl; Mol wt: 439.3882

ACTION – PARP (poly[ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase) inhibitor, potentially useful for the treatment of neurological and neurodegenerative disorders including cerebral ischemia, traumatic brain injury, stroke, Huntington’s disease, Parkinson’s disease and epilepsy. Other exemplified heterocyclic substituted benzimidazoles include the following:



Compound	R1	X	Formula
297070	6-(4-Pr-1-Piz)-3-Pyr		C ₂₀ H ₂₄ N ₆ O
297071	2-[N(Et)2CH2CH2N(Me)]-4-Pyr		C ₂₀ H ₂₆ N ₆ O
297072	6-(4-t-Bu-1-Piz)-3-Pyr		C ₂₁ H ₂₆ N ₆ O
297073	6-(4-Bu-1-Piz)-3-Pyr	HCl	C ₂₁ H ₂₆ N ₆ O.HCl

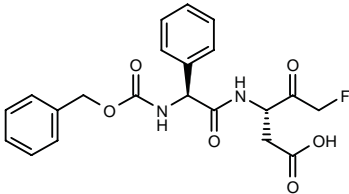
SOURCE – BASF.

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1. Lubisch, W. et al. (BASF AG) *Heterocyclically substd. benzimidazoles, the production and application thereof*. DE 19920936, WO 0068206.

297125

N-Benzyloxycarbonyl-L-phenylglycyl-L-aspartyl-fluoro-methane



C21 H21 F N2 O6; Mol wt: 416.4029

ACTION – A representative compound from a series of dipeptides that are potent inhibitors of caspases and apoptotic cell death. *In vitro*, compound inhibited caspase 3 with an IC₅₀ value of 0.10 μM. When given i.v. to mice, it dose-dependently inhibited anti-Fas antibody-induced mortality, survival being 100% and 42.9% at 1 and 24 h after administration of a dose of 50 mg/kg i.v. Potentially useful for retarding or blocking cell death in a variety of clinical conditions including ischemia, neurodegenerative, cardiovascular and autoimmune diseases and AIDS, for reducing or preventing cell, tissue and organ damage during transplantation, for reducing or preventing alopecia, and for reducing premature skin cell death.

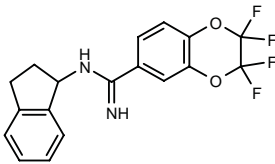
SOURCE – Cytovia (Maxim).

REFERENCES

1. Cai, S.X. et al. (Cytovia, Inc.) *Dipeptide caspase inhibitors and the use thereof*. EP 1076563, US 6153591.

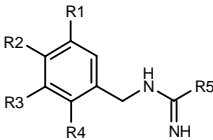
297471

N-(2,3-Dihydro-1H-inden-1-yl)-2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-carboxamidine



C18 H14 F4 N2 O2; Mol wt: 366.3126

ACTION – NMDA antagonist that blocks the NR2B subunit of this receptor. This compound is indicated for the treatment of pain, epilepsy, stroke, anxiety, cerebral ischemia, muscular spasm, Alzheimer’s disease, Huntington’s disease and Parkinson’s disease, and particularly useful for the treatment of neuropathic pain. Other exemplified aryl amidines include the following:



Compound	R1	R2	R3	R4	R5	Formula
297472	H	H	Cl	H	4-(CF3O)-Ph	C ₁₅ H ₁₂ ClF ₃ N ₂ O
297473	H	H	H	OCF3	3,4-(Cl)2-Ph	C ₁₅ H ₁₁ Cl ₂ F ₃ N ₂ O
297474	H	H	OCF3	H	2,1,3-benzothiadiazol-5-yl	C ₁₅ H ₁₁ F ₃ N ₄ OS
297475	Me	H	Me	H	2,2-(F)2-1,3-benzodioxol-5-yl	C ₁₇ H ₁₆ F ₂ N ₂ O ₂
297476	H	H	Cl	H	4-F-Ph	C ₁₄ H ₁₂ ClFN ₂
297477	H	H	H	OCF3	3-CF3-Ph	C ₁₆ H ₁₂ F ₆ N ₂ O
297478	H	H	Cl	H	3,4-(MeO)2-Ph	C ₁₆ H ₁₇ ClN ₂ O ₂
297479	H	OMe	H	H	3,4-(Cl)2-Ph	C ₁₅ H ₁₄ Cl ₂ N ₂ O

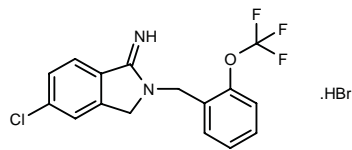
SOURCE – Merck & Co.

REFERENCES

1. Claiborne, C.F. et al. (Merck & Co., Inc.) *Aryl amidines, compsns. containing such cpds. and methods of use*. WO 0067751.

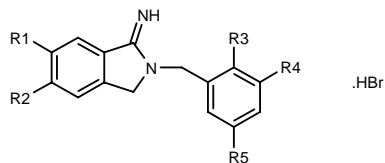
297480

5-Chloro-2-[2-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindol-1-imine hydrobromide



C16 H12 Cl F3 N2 O . HBr; Mol wt: 421.6427

ACTION – NMDA antagonist that blocks the NR2B subunit of this receptor. This compound is indicated for the treatment of pain, epilepsy, stroke, anxiety, cerebral ischemia, muscular spasm, Alzheimer’s disease, Huntington’s disease and Parkinson’s disease, and particularly useful for the treatment of neuropathic pain. Other specifically claimed cyclic amidines include the following:



Compound	R1	R2	R3	R4	R5	Formula
297481	H	Cl	H	Cl	Cl	C ₁₅ H ₁₁ Cl ₃ N ₂ .HBr
297482	Cl	Cl	H	Cl	H	C ₁₅ H ₁₁ Cl ₃ N ₂ .HBr
297483	Cl	Cl	OMe	H	H	C ₁₆ H ₁₄ Cl ₂ N ₂ O.HBr
297484	Cl	Cl	H	OMe	H	C ₁₆ H ₁₄ Cl ₂ N ₂ O.HBr
297485	H	OCF3	OCF3	H	H	C ₁₇ H ₁₂ F ₆ N ₂ O ₂ .HBr
297486	H	OCF3	H	OMe	H	C ₁₇ H ₁₅ F ₃ N ₂ O ₂ .HBr
297487	H	OCF3	H	Me	Me	C ₁₈ H ₁₇ F ₃ N ₂ O.HBr

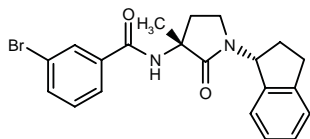
SOURCE – Merck & Co.

REFERENCES

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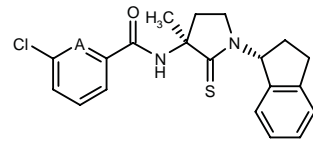
297539

3-Bromo-*N*-[1-[2,3-dihydro-1*H*-inden-1(*R*)-yl]-3(*R*)-methyl-2-oxopyrrolidin-3-yl]benzamide



C21 H21 Br N2 O2; Mol wt: 413.3129

ACTION – Metabotropic glutamate mGluR₅ receptor antagonist indicated for the treatment of neuro-degenerative disorders and pain. Other specifically claimed compounds are:



Compound	A	Formula
297540	CH	C ₂₁ H ₂₁ ClN ₂ OS
297541	N	C ₂₀ H ₂₀ ClN ₃ OS

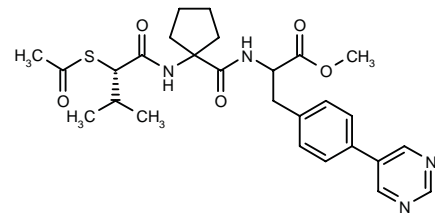
SOURCE – Lilly.

REFERENCES

1. Clark, B.P. et al. (Eli Lilly and Company) *Metabotropic glutamate receptor antagonists*. WO 0069816.

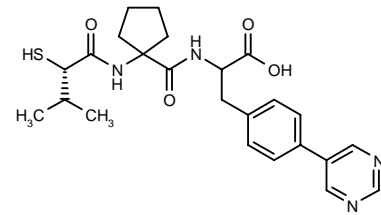
299797

N-[1-[2(*S*)-(Acetylsulfanyl)-3-methylbutanamido]cyclopentylcarbonyl]-4-(5-pyrimidinyl)-DL-phenylalanine methyl ester



C27 H34 N4 O5 S; Mol wt: 526.6546

ACTION – Orally active thioacetate and methyl double ester prodrug of a potent endothelin-converting enzyme-1 (ECE-1) inhibitor (IC₅₀ = 120 nM). The prodrug strongly inhibited the big ET-1-induced pressor response in conscious rats after oral administration, giving a 45% reduction at the dose of 20 mgEq/kg at 2 h. Potentially useful for the treatment of disorders associated with overproduction of ET-1 such as cerebral vasospasm, stroke, asthma and cardiac and renal failure. The active compound is:



299936: C24 H30 N4 O4 S

SOURCE – Novartis.

REFERENCES

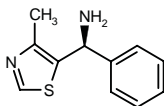
1. Fink, C.A. and Firoozina, F. (Novartis AG;Novartis-Erfindungen VmbH) *Certain heteroaryl substd. thiol inhibitors of endothelin-converting enzyme*. EP 1080104, WO 9955723.

2. Firooznia, F. et al. *Synthesis and biological activity of novel potent endothelin-converting enzyme-1 inhibitors*. Bioorg Med Chem Lett 2001, 11(3): 375.

(-)-(S)-AR-A008055**296622**

(-)-(S)-1-(4-Methylthiazol-5-yl)-1-phenylmethanamine

(-)-(S)-1-(4-Methylthiazol-5-yl)-1-phenylmethylamine



C11 H12 N2 S; Mol wt: 204.2958

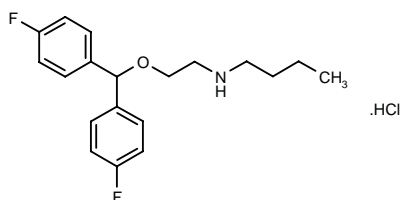
ACTION – Neuroprotective GABA_{mimetic} agent, an analogue of clomethiazole proven to inhibit ischemia-induced glutamate efflux in cerebral cortical tissue exposed to a hypoxic–hypoglycemic medium (52% inhibition at 100 μ M), an effect which was completely reversed by picrotoxin but not by bicuculline, demonstrating that compound potentiates GABA_A receptor functions through an effect on GABA_A chloride channels. In a model of transient global cerebral ischemia in gerbils, a dose of 600 μ mol/kg i.p. 60 min after bilateral carotid occlusion strongly and significantly attenuated hippocampal CA1 degeneration. Moreover, compound, like clomethiazole, showed a separation between neuroprotective activity and sedative or anticonvulsant activity in rats.

SOURCE – AstraZeneca.**REFERENCES**

- Colado, M.I. et al. *Prevention of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) induced neurodegeneration by the clomethiazole analogue AR-A008055*. Br J Pharmacol 2001, 133(Suppl.): Abst 133P.
- Green, A.R. et al. *The sedative and anticonvulsant properties of the enantiomers of AR-A008055, GABA_{mimetic} compounds with neuroprotective activity*. Br J Pharmacol 2000, 131(Suppl.): Abst 203P.
- Nelson, R. et al. *The neuroprotective effect of (S)-AR-A008055, an analogue of Zendra and GABA_{mimetic} agent, in global ischaemia*. Stroke 2000, 31(11): Abst 659.
- Nelson, R.M. et al. *AR-A008055, a clomethiazole analogue, is neuroprotective in a global ischaemia model in vivo and inhibits ischaemia-induced glutamate release in vitro*. Br J Pharmacol 2000, 131(Suppl.): Abst 204P.

LY-393613**299719**

N-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-butanamine hydrochloride



C19 H23 F2 N O . HCl; Mol wt: 355.8536

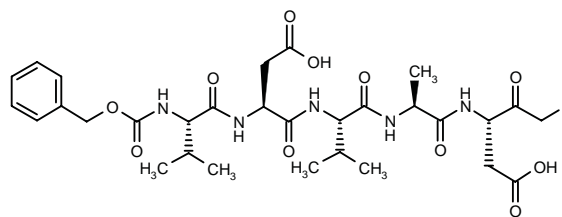
ACTION – Neuronal (N/P/Q-type) voltage-sensitive Ca²⁺ channel blocker with antiischemic activity in a model of ET-1-induced focal cerebral ischemia in rats. Compound given at a dose of 15 mg/kg i.p. before and after ischemia was able to decrease glutamate but not dopamine release, and it reduced infarct volume when given before occlusion. These effects were not due to a direct blockade of the vasoconstrictive action of ET-1, nor to alterations in striatal blood flow. For comparison, nimodipine and verapamil failed to provide neuroprotection when given after occlusion.

SOURCE – Lilly.**REFERENCES**

- Bogaert, L. et al. *The effects of LY393613, nimodipine and verapamil, in focal cerebral ischaemia*. Eur J Pharmacol 2001, 411(1-2): 71.

Z-VDVAD-FMK**300147**

N-(Benzyloxycarbonyl)-L-valyl-L-aspartyl-L-valyl-L-alanyl-L-aspartyl-fluoromethane



C30 H42 F N5 O11; Mol wt: 667.6838

ACTION – Antiapoptotic agent, an irreversible caspase 2 inhibitor with additional activity against caspase 3 and caspase 7, proven to significantly reduce oxyhemoglobin-induced cell detachment, abolish oxyhemoglobin-induced DNA ladders and prevent oxyhemoglobin-induced cleavage of poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase) in cultured bovine brain microvascular endothelial cells. Potentially useful for the treatment of cerebral vasospasm after subarachnoid hemorrhage.

SOURCE – University of Mississippi, Oxford, MS (US).**REFERENCES**

- Anuradha, C.D. et al. *RGD peptide-induced apoptosis in human leukemia HL-60 cells requires caspase-3 activation*. Cell Biol Toxicol 2000, 16(5): 275.
- Gamen, S. et al. *Doxorubicin treatment activates a Z-VAD-sensitive caspase, which causes $\Delta\Psi_m$ loss, caspase-9 activity, and apoptosis in Jurkat cells*. Exp Cell Res 2000, 258(1): 223.
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- Meguro, T. et al. *Caspase inhibitors attenuate oxyhemoglobin-induced apoptosis in endothelial cells*. Stroke 2001, 32(2): 561.
- Robertson, J.D. et al. *Distinct pathways for stimulation of cytochrome C release by etoposide*. J Biol Chem 2000, 275(42): 32438.

RESPIRATORY DRUGS

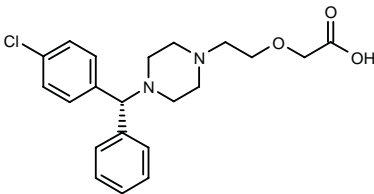
TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

LEVOCETIRIZINE+

269103

(*R*)-2-[2-[4-[1-(4-Chlorophenyl)-1-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid

(-)-Cetirizine



C21 H25 Cl N2 O3; Mol wt: 388.8925

ACTION – Potent and selective peripheral histamine H₁ receptor antagonist, the (*R*)-enantiomer of cetirizine.

INDICATION – Treatment of allergic rhinitis (seasonal and perennial) and urticaria.

PRESENTATION – Film-coated tablets, 5 mg levocetirizine dihydrochloride.

PROPRIETARY NAME – *Xusal* (DE).

SOURCES – Sepracor; marketed by UCB.

REFERENCES

1. Cossement, E. et al. (UCB SA) *Enantiomers of 1-[4-(chlorophenyl)phenylmethyl]-4-(methylphenyl)sulfonyl piperazine*. EP 0617028.

2. Cossement, E. et al. (UCB SA) *Process for preparation of a 1-piperazine-ethoxyacetic acid*. GB 2225321.

3. Gray, N.M. (Sepracor Inc.) *Compsns. for treating allergic disorders using (-) cetirizine*. EP 0663828, JP 1996501561, US 5698558, WO 9406429.

4. Gray, N.M. (Sepracor Inc.) *Methods and compsns. for treating allergic disorders using optically pure (+) cetirizine*. EP 0661975, JP 1996501562, WO 9406430.

5. Van De Venne, H. and Martin, J.-P. (UCB SA) *Pharmaceutical compsns. for the treatment of rhinitis*. GB 2311940.

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7. Devalia, J.L. et al. *A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and UCB 28557 on histamine-induced cutaneous responses in healthy adult volunteers*. Allergy 2001, 56(1): 50.

8. Pflum, D.A. et al. *A large-scale synthesis of enantiomerically pure cetirizine dihydrochloride using preparative chiral HPLC*. Org Process Res Dev 2001, 5(2): 110.

9. Wang, D.Y. et al. *Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers*. Allergy 2001, 56(4): 339.

10. *New therapeutic option for allergies available from UCB in Germany*. DailyDrugNews.com (Daily Essentials) 2001, Feb 16.

12. *Sepracor and UCB reach Zyrtec isomer licensing agreement*. DailyDrugNews.com (Daily Essentials) 1999, June 3.

13. *Sepracor makes progress in first quarter of 2001*. DailyDrugNews.com (Daily Essentials) 2001, April 26.

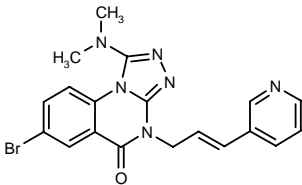
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+Drug Data Rep 1999, 021(07): 0591.

ASTHMA THERAPY

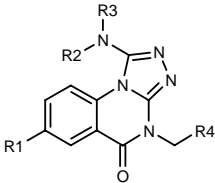
296754

7-Bromo-1-(dimethylamino)-4-[3-(3-pyridinyl)-2(*E*)-propenyl][1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one



C19 H17 Br N6 O; Mol wt: 425.2883

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.079 μM against enzyme obtained from human U937 cells) and TNF-α production, with potential as an antiinflammatory, antiallergic, antiasthmatic and bronchodilating agent. Compound was shown to inhibit lipopolysaccharide-stimulated TNF-α production both *in vitro* in human leukocytes (IC₅₀ = 3.4 μM) and *in vivo* in rats (98% inhibition at 10 mg/kg p.o.). Other exemplified compounds from this series of 1-aminotriazolo[4,3-*a*]quinazoline-5-ones and -5-thiones include the following:



Compound	R1	R2	R3	R4	Formula
296755	Me	Me	Me	3-Pyr-CH=CH	C ₂₀ H ₂₀ N ₆ O
296756	Me	-(CH2)4-		3,4-(MeO)2-Ph	C ₂₃ H ₂₅ N ₆ O ₃
296757	Me	Me	Me	4-CN-Ph	C ₂₀ H ₁₈ N ₆ O
296758	Br	Me	Me	CH=CHPh	C ₂₀ H ₁₈ BrN ₆ O
296759	Me	-(CH2)4-		CH=CHPh	C ₂₃ H ₂₃ N ₆ O
296760	Br	Me	Me	4-CN-Ph	C ₁₉ H ₁₅ BrN ₆ O
296761	Br	-(CH2)6-		3-Pyr	C ₂₁ H ₂₁ BrN ₆ O
296762	Me	-(CH2)4-		4-CN-Ph	C ₂₂ H ₂₀ N ₆ O
296763	Me	Me	Me	CH=CHPh	C ₂₁ H ₂₁ N ₆ O
296764	Br	-(CH2)4-		4-CN-Ph	C ₂₁ H ₁₇ BrN ₆ O
296765	Br	-(CH2)6-		3,4-(MeO)2-Ph	C ₂₄ H ₂₆ BrN ₆ O ₃

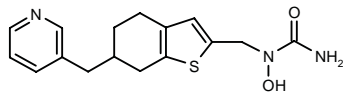
SOURCE – Pfizer.

REFERENCES

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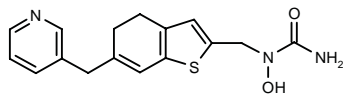
296905

N-Hydroxy-*N*-[6-(3-pyridinylmethyl)-4,5,6,7-tetrahydro-benzothien-2-ylmethyl]urea



C16 H19 N3 O2 S; Mol wt: 317.4111

ACTION – Antiasthmatic, antiallergic and antiinflammatory agent, a dual thromboxane synthase and 5-lipoxygenase inhibitor. *In vitro*, compound inhibited LTB₄ and TxB₂ production in rat abdominal exudate neutrophils with IC₅₀ values of 0.1 and 0.2 μM, respectively. Another compound from this series of *N*-hydroxyurea derivatives is:



296906: C16 H17 N3 O2 S

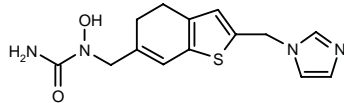
SOURCE – Nikken Chemicals.

REFERENCES

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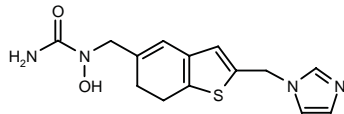
296907

N-Hydroxy-*N*-[2-(1*H*-imidazol-1-ylmethyl)-4,5-dihydro-benzothien-6-ylmethyl]urea



C14 H16 N4 O2 S; Mol wt: 304.3724

ACTION – Antiasthmatic, antiallergic and antiinflammatory agent, a dual thromboxane synthase and 5-lipoxygenase inhibitor. *In vitro*, compound inhibited LTB₄ and TxB₂ production in rat abdominal exudate neutrophils with IC₅₀ values of 1 and 0.01 μM, respectively. Another compound from this series of *N*-hydroxyurea derivatives is:



296908: C14 H16 N4 O2 S

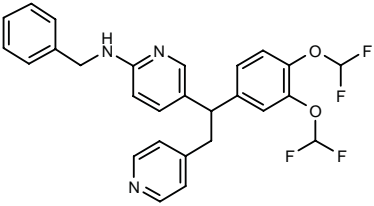
SOURCE – Nikken Chemicals.

REFERENCES

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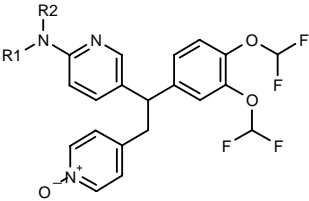
297098

N-Benzyl-5-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]pyridin-2-amine

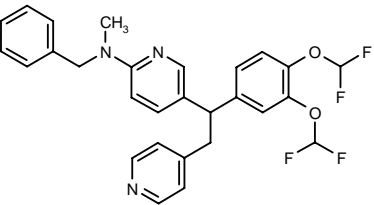


C27 H23 F4 N3 O2; Mol wt: 497.4897

ACTION – Agent for the treatment and prophylaxis of asthma and other inflammatory conditions, a selective inhibitor of phosphodiesterase type 4 (PDE4). *In vitro*, compound inhibited human recombinant PDE4a-mediated hydrolysis of cAMP with an IC₅₀ value of 0.75 nM. Other exemplified compounds from this series of heterosubstituted pyridine derivatives include the following:



Compound	R1	R2	Formula
297099	H	PhC(Me)2	C ₂₉ H ₂₇ F ₄ N ₃ O ₃
297101	Me	4-MeO-Ph	C ₂₈ H ₂₅ F ₄ N ₃ O ₄



297100: C28 H25 F4 N3 O2

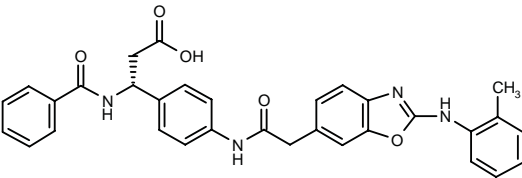
SOURCE – Merck Frosst.

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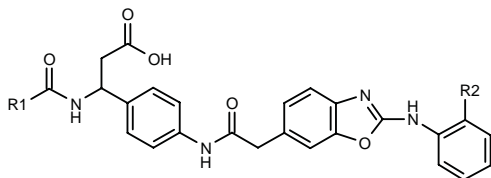
297104

3-Benzamido-3(*R*)-[4-[2-[2-(2-methylphenylamino)-benzoxazol-6-yl]acetamido]phenyl]propionic acid



C32 H28 N4 O5; Mol wt: 548.5962

ACTION – An inhibitor of the interaction of VCAM-1 and fibronectin with the integrin receptor VLA-4 ($\alpha_4\beta_1$), with potential in the treatment of diseases mediated by $\alpha_4\beta_1$ -regulated cell adhesion such as asthma and other inflammatory diseases such as joint inflammation and inflammatory bowel disease. Other substituted bicyclic compounds include the following:



Compound	R1	R2	Formula
297105	5-Me-3-isoxazolyl	Me	C ₃₀ H ₂₇ N ₅ O ₆
297106	5-Me-3-isoxazolyl	OMe	C ₃₀ H ₂₇ N ₅ O ₇
297107	5-Me-3-isoxazolyl	Cl	C ₂₉ H ₂₄ ClN ₅ O ₆
297108	4-Pyr	Cl	C ₃₀ H ₂₄ ClN ₅ O ₅
297109	2-thienyl	Me	C ₃₀ H ₂₆ N ₄ O ₅ S

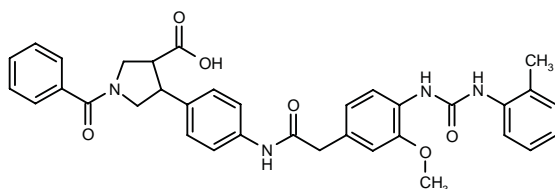
SOURCE – Aventis Pharma.

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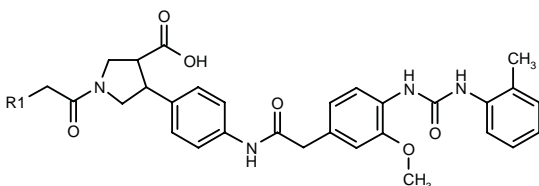
297110

1-Benzoyl-4-[4-[2-[3-methoxy-4-[3-(2-methylphenyl)-ureido]phenyl]acetamido]phenyl]pyrrolidine-3-carboxylic acid



C35 H34 N4 O6; Mol wt: 606.6756

ACTION – An inhibitor of the interaction of VCAM-1 and fibronectin with the integrin receptor VLA-4 ($\alpha_4\beta_1$), with potential in the treatment of diseases mediated by $\alpha_4\beta_1$ -regulated cell adhesion such as asthma and other inflammatory diseases such as joint inflammation and inflammatory bowel disease. Other compounds from this series of substituted pyrrolidines include the following:



Compound	R1	Formula
297111	H	C ₃₀ H ₃₂ N ₄ O ₆
297112	CH ₂ CO ₂ H	C ₃₂ H ₃₄ N ₄ O ₈

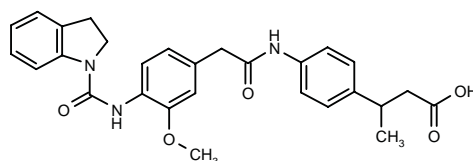
SOURCE – Aventis Pharma.

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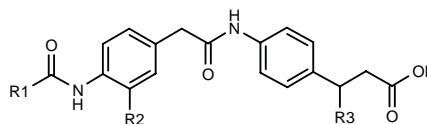
297137

3-[4-[2-[4-(2,3-Dihydro-1H-indol-1-ylcarboxamido)-3-methoxyphenyl]acetamido]phenyl]butyric acid



C28 H29 N3 O5; Mol wt: 487.5531

ACTION – An inhibitor of the interaction of VCAM-1 and fibronectin with the integrin receptor VLA-4 ($\alpha_4\beta_1$) with potential in the treatment of diseases mediated by $\alpha_4\beta_1$ -regulated cell adhesion such as asthma and other inflammatory diseases such as joint inflammation and inflammatory bowel disease. Other compounds from this series of urea derivatives include the following:



Compound	R1	R2	R3	Formula
297138	N(Me)Ph	OMe	Me	C ₂₇ H ₂₉ N ₃ O ₅
297139	2,3-dihydro-1-indolyl	H	NHCOPh	C ₃₃ H ₃₀ N ₄ O ₅
297140	2,3-dihydro-1-indolyl	H	NHAc	C ₂₈ H ₂₈ N ₄ O ₅
297142	2,3-dihydro-1-indolyl	OMe	NHAc	C ₂₉ H ₃₀ N ₄ O ₆
297143	N(Me)CH ₂ H ₂ Ph	OMe	NHAc	C ₃₀ H ₃₄ N ₄ O ₆
297144	N(Me)CH ₂ Ph	OMe	NHAc	C ₂₉ H ₃₂ N ₄ O ₆

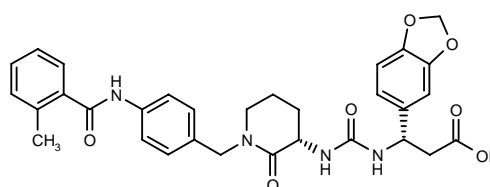
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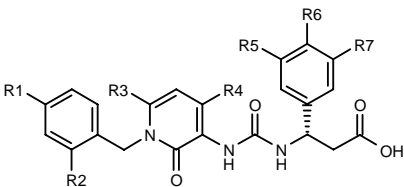
297145

3(S)-(1,3-Benzodioxol-5-yl)-3-[3-[1-[4-(2-methylbenz-amido)benzyl]-2-oxopiperidin-3(S)-yl]ureido]propionic acid



C31 H32 N4 O7; Mol wt: 572.6148

ACTION – An inhibitor of the binding of VCAM-1 and fibronectin to $\alpha_v\beta_1$ integrin with potential in the treatment of a broad range of diseases including asthma, atherosclerosis, rheumatoid arthritis, allergy, multiple sclerosis, lupus, inflammatory bowel disease, graft rejection, contact hypersensitivity, type 1 diabetes and cancer. *In vitro*, compound inhibited the adhesion of Ramos cells to CS1 peptide-coated wells with an IC₅₀ value of 0.3 nM. Other exemplified compounds from this series of carboxylic acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
297148	2-Me-Ph-CONH	H	H	H	H	-OCH2O-		C ₃₁ H ₂₈ N ₄ O ₇
297149	H	Cl	H	Pr	H	Me	H	C ₂₆ H ₂₈ ClN ₃ O ₄
297150	H	Cl	H	Me	H	Me	H	C ₂₄ H ₂₄ ClN ₃ O ₄
297151	H	H	Me	OCH2Ph	H	Me	H	C ₃₁ H ₃₁ N ₃ O ₅
297152	H	Cl	H	Me	H	OMe	H	C ₂₄ H ₂₄ ClN ₃ O ₅
297153	H	Cl	H	4-morpholinyl	H	Me	H	C ₂₇ H ₂₉ ClN ₄ O ₅
297154	H	Cl	H	t-BuNH	H	Me	H	C ₂₇ H ₃₁ ClN ₄ O ₄
297155	H	Cl	H	4-Me-1-Piz	H	Me	H	C ₂₈ H ₃₂ ClN ₃ O ₄
297156	H	Cl	H	OH	H	OMe	H	C ₂₃ H ₂₂ ClN ₃ O ₆
297157	H	Cl	H	OH	H	H	OMe	C ₂₃ H ₂₂ ClN ₃ O ₆
297158	H	Cl	H	OH	OMe	H	OMe	C ₂₄ H ₂₄ ClN ₃ O ₇
297159	H	Cl	H	NHCON(Et)-CONHEt	H	Me	H	C ₂₉ H ₃₃ ClN ₆ O ₆
297160	H	Cl	H	1-azetidiny	H	Me	H	C ₂₆ H ₂₇ ClN ₄ O ₄
297162	H	Cl	H	O(CH2-CH2O)3Me	H	Me	H	C ₃₀ H ₃₆ ClN ₃ O ₈

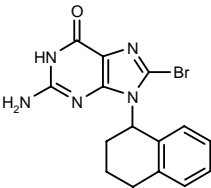
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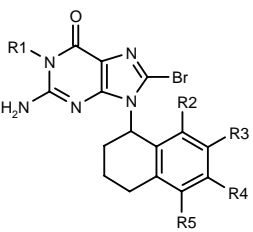
297172

2-Amino-8-bromo-9-(1,2,3,4-tetrahydronaphthalen-1-yl)-guanine

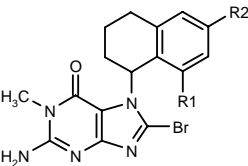


C15 H14 Br N5 O; Mol wt: 360.2136

ACTION – An inhibitor of phosphodiesterase type 7 (PDE7) with potential for the treatment of inflammatory and autoimmune diseases, particularly asthma, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, chronic bronchitis, allergic rhinitis, inflammatory bowel disease, pancreatitis, multiple sclerosis, systemic lupus erythematosus, transplant rejection, graft-versus-host disease, restenosis following angioplasty and atherosclerosis. Other specifically claimed compounds from this series of 9-(1,2,3,4-tetrahydronaphthalen-1-yl)-1,9-dihydropurin-6-one derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
297174	H	H	H	Br	H	C ₁₅ H ₁₃ Br ₂ N ₆ O
297175	H	Br	H	H	H	C ₁₅ H ₁₃ Br ₂ N ₆ O
297178	Me	H	H	Br	H	C ₁₆ H ₁₅ Br ₂ N ₆ O
297179	Me	Br	H	H	H	C ₁₆ H ₁₅ Br ₂ N ₆ O
297183	H	H	OMe	H	H	C ₁₆ H ₁₆ BrN ₅ O ₂
297187	H	H	H	H	OMe	C ₁₆ H ₁₆ BrN ₅ O ₂
297188	H	H	NO2	H	H	C ₁₅ H ₁₃ BrN ₆ O ₃
297189	H	H	CO2Me	H	H	C ₁₇ H ₁₆ BrN ₅ O ₃
297190	H	H	CO2H	H	H	C ₁₆ H ₁₄ BrN ₅ O ₃
297191	H	H	CONHOH	H	H	C ₁₆ H ₁₅ BrN ₆ O ₃



Compound	R1	R2	Formula
297180	H	Br	C ₁₆ H ₁₅ Br ₂ N ₆ O
297182	Br	H	C ₁₆ H ₁₅ Br ₂ N ₆ O

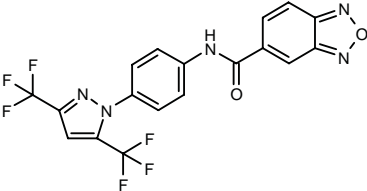
SOURCE – Darwin Discovery.

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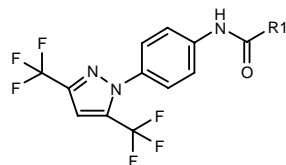
297332

N-[4-[3,5-Bis(trifluoromethyl)-1 H-pyrazol-1-yl]phenyl]-2,1,3-benzoxadiazole-5-carboxamide



C18 H9 F6 N5 O2; Mol wt: 441.2901

ACTION – An inhibitor of calcium (Ca²⁺) release-activated calcium (Ca²⁺) channels (CRACC) as well as of the production of IL-2, potentially useful in the treatment of bronchial asthma, psoriasis, atopic dermatitis, inflammatory bowel disease, peptic ulcer, nephritis, hepatitis, pancreatitis, rheumatoid arthritis, osteoarthritis, transplant rejection, cancer, arteriosclerosis, ischemia–reperfusion disorders and cerebral and myocardial infarction. Other exemplified compounds from this series of pyrazole derivatives include the following:



Compound	R1	Formula
297334	6-(4-morpholinyl)-3-Pyr	C ₂₁ H ₁₇ F ₆ N ₅ O ₂
297335	2-MeS-3-Pyr	C ₁₈ H ₁₂ F ₆ N ₄ OS
297336	4-OH-2-quinolyl	C ₂₁ H ₁₂ F ₆ N ₄ O ₂
297338	3-Me-2-furyl	C ₁₇ H ₁₁ F ₆ N ₃ O ₂
297340	4-indolyl	C ₂₀ H ₁₂ F ₆ N ₄ O
297342	1-Me-2-indolyl	C ₂₁ H ₁₄ F ₆ N ₄ O
297343	3-OH-2-quinoxaliny	C ₂₀ H ₁₁ F ₆ N ₅ O ₂
297345	6-[N(Et)2CH2CH2N(Et)]-3-Pyr	C ₂₈ H ₂₈ F ₆ N ₆ O
297347	3-Pyr-CH=CH	C ₁₉ H ₁₂ F ₆ N ₄ O
297349	2-Cl-6-MeO-4-Pyr	C ₁₈ H ₁₁ ClF ₆ N ₄ O ₂
297350	2-(1,2,3,4-tetrahydro-2-isoquinolyl)-3-Pyr	C ₂₆ H ₁₉ F ₆ N ₅ O
297351	6-(4-Me-1-Pip)-3-Pyr	C ₂₃ H ₂₁ F ₆ N ₅ O

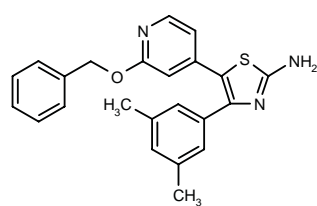
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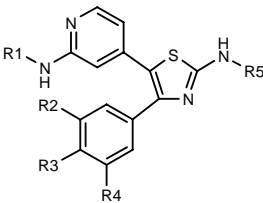
297419

5-[2-(Benzyloxy)pyridin-4-yl]-4-(3,5-dimethylphenyl)-thiazol-2-amine



C23 H21 N3 O S; Mol wt: 387.5049

ACTION – Potent adenosine A₃ receptor antagonist, as demonstrated by an IC₅₀ value of 11.6 nM in a human adenosine A₃ receptor binding assay, also reported to inhibit p38 MAP kinase (IC₅₀ = 0.43 μM) and TNF-α production. Potentially useful for the treatment of a broad range of disorders including asthma, allergic diseases, cerebrovascular disorders, head injury, cerebral edema, inflammation, autoimmune diseases and Alzheimer's disease. Other exemplified compounds from this series of 5-pyridyl-1,3-azole derivatives include the following:



Compound	R1	R2=R4	R3	R5	Formula
297422	COPh	H	OMe	COPh	C ₂₉ H ₂₂ N ₄ O ₃ S
297424	3-Pyr-CO	H	OMe	3-Pyr-CO	C ₂₇ H ₂₀ N ₆ O ₃ S
297426	COPh	H	OMe	H	C ₂₂ H ₁₈ N ₄ O ₂ S
297427	COPh	Me	H	H	C ₂₃ H ₂₀ N ₄ OS
297428	CH2Ph	Me	H	H	C ₂₃ H ₂₂ N ₄ S

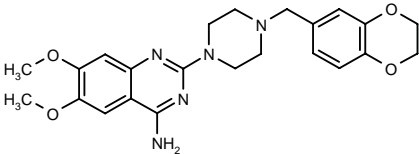
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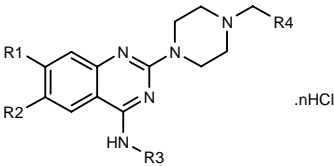
297431

2-[4-(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine



C23 H27 N5 O4; Mol wt: 437.4973

ACTION – Agent for the treatment of allergic diseases such as asthma, atopic dermatitis and allergic rhinitis and autoimmune diseases such as rheumatoid arthritis, osteoarthritis and systemic lupus erythematosus with IgE production-inhibitory activity, as demonstrated *in vitro* in lipopolysaccharide- and IL-4-stimulated B-cell fractions from murine spleen cells (89% inhibition at 10 μM). A representative compound from a series of quinazoline derivatives, wherein the following are also included:



Compound	R1=R2	R3	R4	n	Formula
297433	OMe	H	2-Pyr	3	C ₂₀ H ₂₄ N ₆ O ₂ .3HCl
297436	OMe	H	3,4-(MeO)2-Ph	2	C ₂₃ H ₂₉ N ₅ O ₄ .2HCl
297438	OMe	H	1-Naph	0	C ₂₅ H ₂₇ N ₅ O ₂
297439	OMe	H	2,3,4-(MeO)3-Ph	0	C ₂₄ H ₃₁ N ₅ O ₅
297440	H	CH2CH2Ph	Ph	1	C ₂₇ H ₂₉ N ₅ .HCl
297441	H	CH2CH2Ph	2-MeO-Ph-NHCH2	0	C ₂₉ H ₃₄ N ₆ O
297442	H	CH2CH2Ph	2-MeO-Ph-NHCH2CH2	0	C ₃₀ H ₃₆ N ₆ O
297443	OMe	H	4-(CO2Me)-Ph	0	C ₂₃ H ₂₇ N ₅ O ₄
297445	OMe	H	4-OH-PhCH2	0	C ₂₂ H ₂₇ N ₅ O ₃
297446	OMe	H	1,3-dioxo-2-iso-indoliny-(CH2)3	0	C ₂₆ H ₃₀ N ₆ O ₄
297448	OMe	4-[1,3-dioxo-2-iso-indoliny-(CH2)4]-1-Piz	3,4-(MeO)2-Ph	0	C ₃₉ H ₄₈ N ₈ O ₆

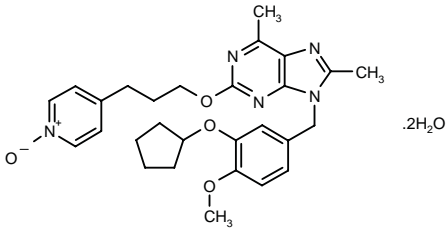
SOURCE – Sumitomo Pharmaceuticals.

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297461

9-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6,8-dimethyl-2-[3-(1-oxidopyridin-4-yl)propoxy]-9*H*-purine dihydrate



C28 H33 N5 O4 . 2H2O; Mol wt: 539.6293

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with an IC₅₀ of 3.41 nM when tested for inhibition of PDE4 from human U937 cells. Potentially useful for the treatment of inflammatory disorders, particularly asthma and chronic obstructive lung disease.

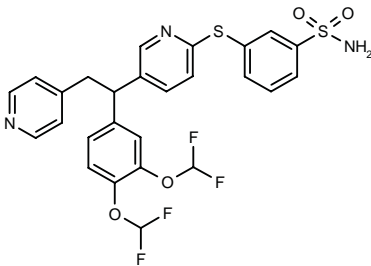
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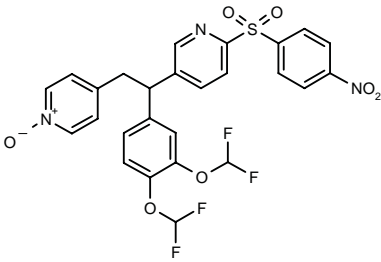
297508

3-[5-[1-[3,4-Bis(difluoromethoxy)phenyl]-2-(4-pyridinyl)ethyl]pyridin-2-ylsulfanyl]benzenesulfonamide



C26 H21 F4 N3 O4 S2; Mol wt: 579.5929

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor proven to inhibit human recombinant PDE4A-mediated hydrolysis of cAMP (IC₅₀ = 5.45 nM). This compound is especially useful for the treatment or prevention of inflammatory conditions, in particular asthma. Another exemplified heterosubstituted pyridine derivative is:



297509: C26 H19 F4 N3 O7 S

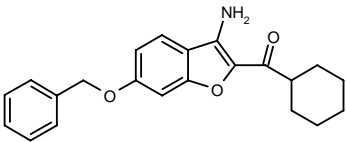
SOURCE – Merck Frosst.

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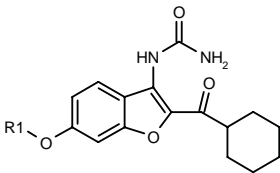
297523

1-(3-Amino-6-benzyloxybenzofuran-2-yl)-1-cyclohexyl-methanone



C22 H23 N O3; Mol wt: 349.4277

ACTION – Antiinflammatory agent that inhibits the production of superoxide by polymorphonuclear leukocytes and TNF- α release in human monocytes in response to a variety of stimuli. These effects are suggested to be mediated by an increase in cellular cAMP levels by inhibition of phosphodiesterase type 4 (PDE4). Other compounds from this series of cycloalkyl substituted 3-urea-benzofuran and -pyridofuran derivatives are:



Compound	R1	Formula
297524	CH2Ph	C ₂₃ H ₂₄ N ₂ O ₄
297525	H	C ₁₆ H ₁₈ N ₂ O ₄
297526	Me	C ₁₇ H ₂₀ N ₂ O ₄
297527	SO2Me	C ₁₇ H ₂₀ N ₂ O ₆ S
297529	CH2C(=CH2)CH2OH	C ₂₀ H ₂₄ N ₂ O ₅
297530	allyl	C ₁₉ H ₂₂ N ₂ O ₄
297531	CH2CH(OH)CH2OH	C ₁₉ H ₂₄ N ₂ O ₆

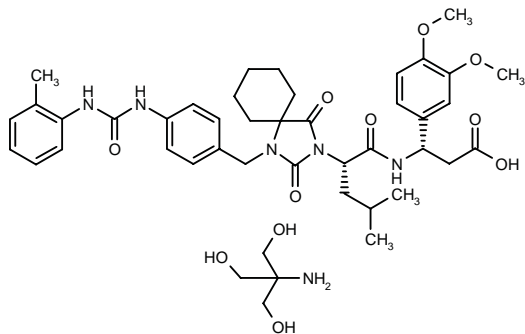
SOURCE – Bayer.

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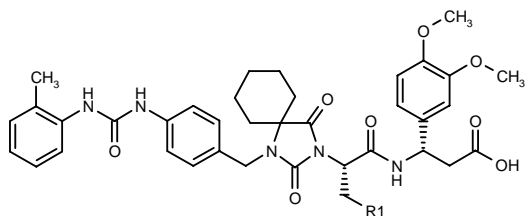
297536

3(S)-(3,4-Dimethoxyphenyl)-3-[4-methyl-2(S)-[1-[4-[3-(2-methylphenyl)ureido]benzyl]-2,4-dioxo-1,3-diazaspiro[4.5]dec-3-yl]pentanamido]propionic acid tromethamine salt



C40 H49 N5 O8 . C4 H11 N O3; Mol wt: 848.9890

ACTION – Inhibitor of leukocyte adhesion and/or VLA-4 antagonist, particularly useful for the treatment of inflammatory conditions such as rheumatoid arthritis and allergic disorders. It was active in a U937/VCAM-1 cell adhesion test with an IC₅₀ of 0.6 nM. Other exemplified spiroimidazolidine derivatives include the following:



Compound	R1	Formula
297537	i-Pr	C ₄₀ H ₄₉ N ₅ O ₈
297538	cyclopropyl	C ₄₀ H ₄₇ N ₅ O ₈

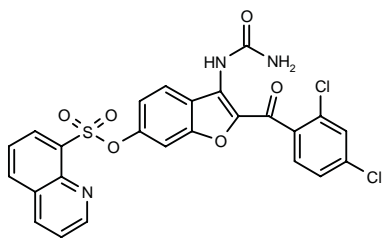
SOURCE – Aventis Pharma.

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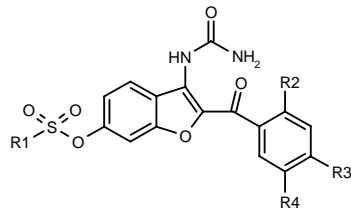
297726

8-Quinolinesulfonic acid 2-(2,4-dichlorobenzoyl)-3-ureido-benzofuran-6-yl ester



C25 H15 Cl2 N3 O6 S; Mol wt: 556.3805

ACTION – Agent for the treatment of acute and chronic inflammatory disorders and autoimmune diseases that inhibits the production of superoxide by polymorphonuclear leukocytes and TNF- α release from human monocytes in response to a variety of stimuli, but potentiates IL-10 release. These effects are suggested to be mediated by an increase in cellular cAMP levels via inhibition of phosphodiesterase type 4 (PDE4). This compound inhibited fMLP-stimulated superoxide radical anion production (IC₅₀ = 0.001 μ M) and PDE4 in human polymorphonuclear leukocytes (IC₅₀ = 0.001 μ M). Other exemplified benzofuranylsulfonates include the following:



Compound	R1	R2	R3	R4	Formula
297727	4-(AcNH)-Ph	H	Cl	H	C ₂₄ H ₁₈ ClN ₃ O ₇ S
297728	5-(2-Pyr)-2-thienyl	Cl	Cl	H	C ₂₅ H ₁₆ Cl ₂ N ₃ O ₆ S ₂
297729	5-Cl-1,3-(Me)2-4-pyrazolyl	F	F	H	C ₂₁ H ₁₅ ClF ₂ N ₄ O ₆ S
297730	1-Me-4-imidazolyl	Me	Me	H	C ₂₂ H ₂₀ N ₄ O ₆ S
297731	N(Me)2	Cl	H	Cl	C ₁₈ H ₁₅ Cl ₂ N ₃ O ₆ S
297732	6-Cl-3-Pyr-CH2	Cl	Cl	H	C ₂₂ H ₁₄ Cl ₃ N ₃ O ₆ S

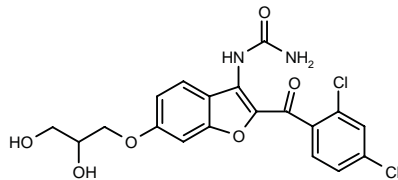
SOURCE – Bayer.

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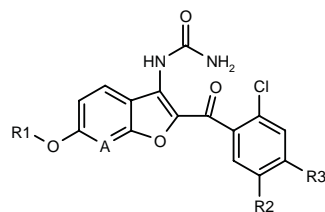
297733

N-[2-(2,4-Dichlorobenzoyl)-6-(2,3-dihydroxypropoxy)-benzofuran-3-yl]urea



C19 H16 Cl2 N2 O6; Mol wt: 439.2494

ACTION – Agent for the treatment of acute and chronic inflammatory disorders and autoimmune diseases that inhibits the production of superoxide by polymorphonuclear leukocytes and TNF- α release from human monocytes in response to a variety of stimuli, but potentiates IL-10 release. These effects are suggested to be mediated by an increase in cellular cAMP levels via inhibition of phosphodiesterase type 4 (PDE4). This compound inhibited fMLP-stimulated superoxide radical anion production (IC₅₀ = 0.008 μ M) and PDE4 in human polymorphonuclear leukocytes (IC₅₀ = 0.006 μ M). Other exemplified benzofuran-yl and pyridofuran-yl urea derivatives include the following:



Compound	R1	R2	R3	A	Isomer	Formula
297734	CH2CH(OH)C(Me)2OH	H	Cl	CH	racemic	C ₂₁ H ₂₀ Cl ₂ N ₂ O ₆
297735	(S ⁺ ,R ⁺)-CH2CH(OH)-CH(OH)CH2OH	H	Cl	CH	racemic	C ₂₀ H ₁₈ Cl ₂ N ₂ O ₇
297736	CH2CH(OH)CH2OH	H	Cl	N	racemic	C ₁₈ H ₁₅ Cl ₂ N ₃ O ₆
297737	(2R)-CH(Ph)CH(OH)CH2OH	H	Cl	CH		C ₂₅ H ₂₀ Cl ₂ N ₂ O ₆
297738	CH(Bu)CH(OH)CH2OH	Cl	H	CH		C ₂₃ H ₂₄ Cl ₂ N ₂ O ₆
297739	CH2C(OH)(CH2F)CH2OH	Cl	H	CH	racemic	C ₂₀ H ₁₇ Cl ₂ FN ₂ O ₆
297740	(CH2)4CH(OH)CH2OH	H	Cl	CH	racemic	C ₂₂ H ₂₂ Cl ₂ N ₂ O ₆

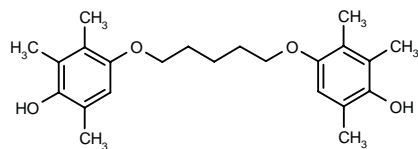
SOURCE – Bayer.

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299597

1,5-Bis(4-hydroxy-2,3,5-trimethylphenoxy)pentane



C23 H32 O4; Mol wt: 372.5018

ACTION – Dual 5-lipoxygenase inhibitor (IC₅₀ = 0.13 μM) and antioxidant (IC₅₀ = 0.44 μM for inhibition of Fe³⁺/ADP-induced lipid peroxidation in rat liver microsomes) with potential for the treatment of inflammation, allergies and cancer.

SOURCE – Tokushima Bunri University, Tokushima (JP).

REFERENCES

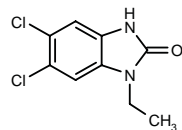
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TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

DCEBIO

299922

5,6-Dichloro-1-ethyl-2,3-dihydro-1*H*-benzimidazol-2-one



C9 H8 Cl2 N2 O; Mol wt: 231.0812

ACTION – Benzimidazolone derivative proven to stimulate chloride secretion, as measured by increase in ⁸⁶Rb⁺ uptake into membrane vesicles derived from human HEK-293 cells expressing intermediate-conductance Ca²⁺-activated potassium channels (hIK1; EC₅₀ = 19 μM). In T84 monolayers, compound enhanced the forskolin-stimulated increase in short-circuit current (EC₅₀ = 24.8 μM) and stimulated Cl⁻ secretion in a concentration-dependent manner (EC₅₀ = 45 μM); the latter effect was almost completely antagonized by the hIK1 blocker charybdotoxin but not by a blocker of cAMP-activated K⁺ channels. Patch-clamp studies in *Xenopus* oocytes expressing hIK1 showed that compound induced a marked and rapid increase in hIK1 activity at concentrations much lower than those required in the ⁸⁶Rb⁺ uptake assay. Potentially useful for the treatment of cystic fibrosis and chronic obstructive pulmonary disease (COPD).

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

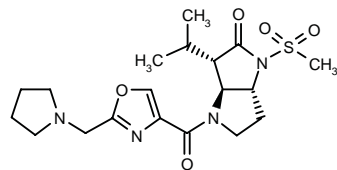
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AGENTS FOR RESPIRATORY DISTRESS SYNDROME

GW-475151

299150

(3*S*,3*aS*,6*aR*)-3-Isopropyl-1-(methylsulfonyl)-4-[2-(1-pyrrolidinylmethyl)oxazol-4-ylcarbonyl]hexahydropyrrolo-[3,2-*b*]pyrrol-2(1*H*)-one



C19 H28 N4 O5 S; Mol wt: 424.5192

ACTION – Human neutrophil elastase inhibitor, a 2,4-disubstituted oxazole with potential for the treatment of respiratory diseases such as acute respiratory distress syndrome, cystic fibrosis, emphysema and chronic bronchitis

SOURCE – GlaxoSmithKline.

REFERENCES

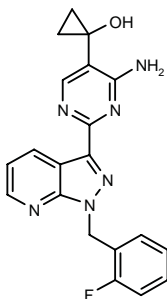
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2. Clarke, G.D.E. et al. (Glaxo Group Ltd.) *Pyrrolopyrrolone derivs. as inhibitors of neutrophil elastase.* WO 9912933.
3. Hermitage, S.A. et al. *An efficient, practical approach to the synthesis of 2,4-disubstituted thiazoles and oxazoles: Application to the synthesis of GW475151.* Org Process Res Dev 2001, 5(1): 37.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

296647

1-[4-Amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl]cyclopropanol



C20 H17 F N6 O; Mol wt: 376.3933

ACTION – Agent for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and stroke, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis, asthma and urogenital system disorders such as prostatic hypertrophy, erectile dysfunction and urinary incontinence that acts by directly stimulating soluble guanylate cyclase and by increasing intracellular cGMP levels, as demonstrated in primary endothelial cells, where compound produced a 22.4-fold increase in intracellular cGMP levels at 1 μ M. In addition, compound inhibited phenylephrine-induced contractions of guinea pig aorta strips (IC_{50} = 290 nM).

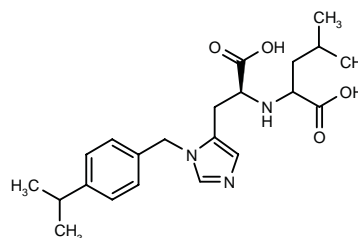
SOURCE – Bayer.

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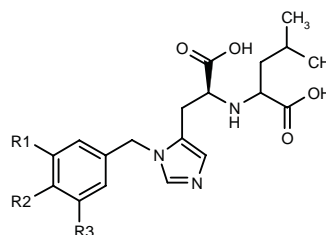
296766

N-[1(*S*)-Carboxy-2-[1-(4-isopropylbenzyl)-1*H*-imidazol-5-yl]ethyl]-DL-leucine isomer A



C22 H31 N3 O4; Mol wt: 401.5039

ACTION – An inhibitor of angiotensin-converting enzyme-2 (ACE-2), a protein having regions of substantial homology to ACE and having angiotensin-cleaving activity, with potential for the treatment of ACE-2-mediated disorders, particularly congestive heart failure and hypertension. *In vitro*, compound inhibited human and rat ACE-2 with IC_{50} values of < 1 μ M and in the range 1-10 μ M, respectively, while inhibiting ACE and carboxypeptidase A with IC_{50} values < 10 μ M. Other exemplified inhibitors include the following:



Compound	R1	R2	R3	Formula
296767	Cl	Cl	H	C ₁₉ H ₂₃ Cl ₂ N ₃ O ₄
296768	H	CN	H	C ₂₀ H ₂₄ N ₄ O ₄
296769	Cl	H	H	C ₁₉ H ₂₄ ClN ₃ O ₄
296770	Cl	H	Cl	C ₁₉ H ₂₃ Cl ₂ N ₃ O ₄
296771	H	Me	H	C ₂₀ H ₂₇ N ₃ O ₄
296772	Me	Me	H	C ₂₁ H ₂₉ N ₃ O ₄
296773	Me	H	H	C ₂₀ H ₂₇ N ₃ O ₄
296774	Me	H	Me	C ₂₁ H ₂₉ N ₃ O ₄
296775	H	OCF ₃	H	C ₂₀ H ₂₄ F ₃ N ₃ O ₅
296776	H	t-Bu	H	C ₂₃ H ₃₃ N ₃ O ₄

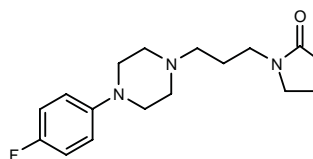
SOURCE – Millennium.

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296868

1-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]pyrrolidin-2-one



C17 H24 F N3 O; Mol wt: 305.3946

ACTION – Human neutrophil elastase inhibitor, a 2,4-disubstituted oxazole with potential for the treatment of respiratory diseases such as acute respiratory distress syndrome, cystic fibrosis, emphysema and chronic bronchitis

SOURCE – GlaxoSmithKline.

REFERENCES

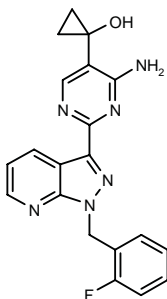
1. Cardwell, K.S. and Hermitage, S.A. (Glaxo Group Ltd.) *Process for preparing oxazole derivs.* WO 0053589.
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

296647

1-[4-Amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl]cyclopropanol



C20 H17 F N6 O; Mol wt: 376.3933

ACTION – Agent for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and stroke, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis, asthma and urogenital system disorders such as prostatic hypertrophy, erectile dysfunction and urinary incontinence that acts by directly stimulating soluble guanylate cyclase and by increasing intracellular cGMP levels, as demonstrated in primary endothelial cells, where compound produced a 22.4-fold increase in intracellular cGMP levels at 1 μ M. In addition, compound inhibited phenylephrine-induced contractions of guinea pig aorta strips (IC_{50} = 290 nM).

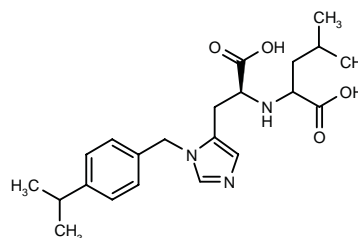
SOURCE – Bayer.

REFERENCES

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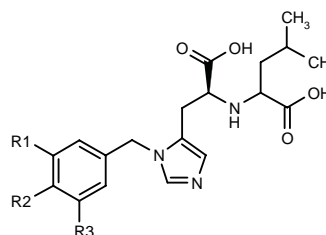
296766

N-[1(*S*)-Carboxy-2-[1-(4-isopropylbenzyl)-1*H*-imidazol-5-yl]ethyl]-DL-leucine isomer A



C22 H31 N3 O4; Mol wt: 401.5039

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296767	Cl	Cl	H	C ₁₉ H ₂₃ Cl ₂ N ₃ O ₄
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296769	Cl	H	H	C ₁₉ H ₂₄ ClN ₃ O ₄
296770	Cl	H	Cl	C ₁₉ H ₂₃ Cl ₂ N ₃ O ₄
296771	H	Me	H	C ₂₀ H ₂₇ N ₃ O ₄
296772	Me	Me	H	C ₂₁ H ₂₉ N ₃ O ₄
296773	Me	H	H	C ₂₀ H ₂₇ N ₃ O ₄
296774	Me	H	Me	C ₂₁ H ₂₉ N ₃ O ₄
296775	H	OCF ₃	H	C ₂₀ H ₂₄ F ₃ N ₃ O ₅
296776	H	t-Bu	H	C ₂₃ H ₃₃ N ₃ O ₄

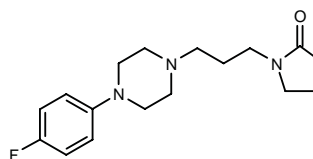
SOURCE – Millennium.

REFERENCES

1. Acton, S.L. et al. (Millennium Pharmaceuticals, Inc.) *ACE-2 inhibiting cpds. and methods of use thereof.* WO 0066104.

296868

1-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]pyrrolidin-2-one



C17 H24 F N3 O; Mol wt: 305.3946

ACTION – Antihypertensive and cardioprotective agent, which exhibited blood pressure-lowering activity both in normotensive and spontaneously hypertensive cats and rats at 10 and 20 µmol/kg i.d. and i.v., while showing little effect on heart rate. Its antihypertensive effects in cats were significantly antagonized (90%) by pretreatment with the α₁-adrenoceptor blocker prazosin. In addition, compound exhibited cardioprotective effects against myocardial stunning at a much smaller dose than that at which antihypertensive effects are observed. Furthermore, in Langendroff-perfused rat heart preparations subjected to global ischemia, it suppressed reperfusion-induced arrhythmia when given at 0.001 µg/ml at the time of reperfusion. LD₅₀ in mice was 147.0 mg/kg i.p. and 562.0 mg/kg p.o. A representative compound from a series of 1-(4-arylpiperazin-1-yl)-3-(2-oxopyrrolidin-1-yl)propanes and 1-(4-arylpiperazin-1-yl)-3-(2-oxopiperidin-1-yl)propanes.

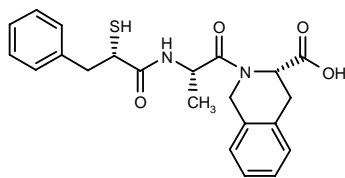
SOURCE – Council of Scientific and Industrial Research (CSIR), New Delhi (IN).

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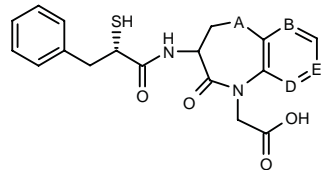
297319

2-[N-[3-Phenyl-2(S)-sulfanylpropionyl]-L-alanyl]-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid

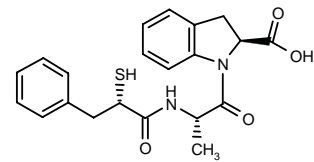


C22 H24 N2 O4 S; Mol wt: 412.5076

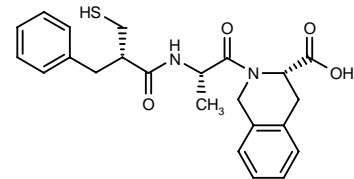
ACTION – Agent for the treatment of hypertension, congestive heart failure and renal diseases, a dual inhibitor of angiotensin-converting enzyme (ACE; IC₅₀ = 0.99 nM or less against enzyme from rabbit lung) and neutral endopeptidase enzyme (NEP; IC₅₀ = 1.0-9.9 nM). Other exemplified condensed heterocyclic compounds include the following:



Compound	A	B	D	E	Formula
297328	CH2	N	CH	CH	C ₂₀ H ₂₁ N ₃ O ₄ S
297329	CH2	CH	N	CH	C ₂₀ H ₂₁ N ₃ O ₄ S
297330	CH2	CH	CH	N	C ₂₀ H ₂₁ N ₃ O ₄ S
297331	S	N	CH	CH	C ₁₉ H ₁₉ N ₃ O ₄ S ₂



297320: C21 H22 N2 O4 S



297322: C23 H26 N2 O4 S

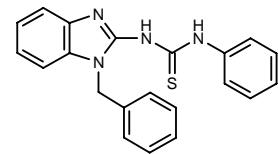
SOURCE – Toa Eiyo.

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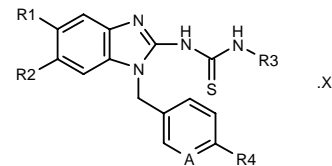
297429

N-(1-Benzyl-1H-benzimidazol-2-yl)-N'-phenylthiourea



C21 H18 N4 S; Mol wt: 358.4672

ACTION – Endothelin-converting enzyme (ECE) inhibitor, as demonstrated by an IC₅₀ value of 0.34 µM against enzyme from rat lung. It is potentially useful for the treatment of endothelin-induced diseases such as hyperlipidemia, arteriosclerosis, cardiovascular and cerebrovascular diseases, nephropathy, pulmonary hypertension, etc. Other exemplified compounds from this series of thiourea derivatives include the following:



Compound	R1=R2	R3	R4	A	X	Formula
297430	H	Me	H	CH		C ₁₆ H ₁₆ N ₄ S
297432	H	4-(NH2CH2)-Ph	H	CH	HCl	C ₂₂ H ₂₁ N ₅ S.HCl
297434	H	1,3-benzodioxol-5-yl	H	N	HCl	C ₂₁ H ₁₇ N ₅ O ₂ S.HCl
297435	OMe	4-(NH2CH2)-Ph	H	CH	HCl	C ₂₄ H ₂₈ N ₅ O ₂ S.HCl
297437	H	4-(NH2CH2)-Ph	OMe	CH	HCl	C ₂₃ H ₂₃ N ₅ OS.HCl

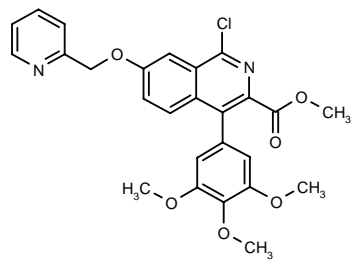
SOURCE – Sumitomo Pharmaceuticals.

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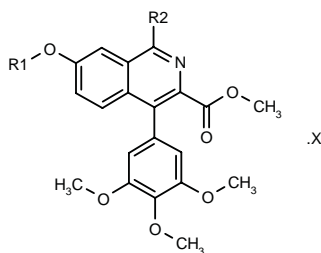
297453

1-Chloro-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)isoquinoline-3-carboxylic acid methyl ester



C26 H23 Cl N2 O6; Mol wt: 494.9287

ACTION – An inhibitor of phosphodiesterase type 5 (PDE5) with potential in the treatment of cardiovascular diseases such as hypertension, angina pectoris, chronic heart failure, pulmonary hypertension, arteriosclerosis and restenosis following PTCA. Other exemplified compounds from this series of isoquinoline derivatives include the following:



Compound	R1	R2	X	Formula
297454	2-Pyr-CH2	O(CH2)3Ph	HCl	C ₃₅ H ₃₄ N ₂ O ₇ .HCl
297455	CH2Ph	OCH2CO2Me		C ₃₀ H ₂₉ NO ₉
297457	2-Pyr-CH2	2-MeO-PhNH	2HCl	C ₃₃ H ₃₁ N ₃ O ₇ .HCl
297458	CH2Ph	3,4,5-(MeO)3-Ph		C ₃₆ H ₃₅ NO ₉
297459	CH2Ph	4-(CH2OH)-1-Pip		C ₃₃ H ₃₆ N ₂ O ₇
297460	CH2Ph	NH(CH2)3OMe	HCl	C ₃₁ H ₃₄ N ₂ O ₇ .HCl
297462	H	4-OH-1-Pip		C ₂₅ H ₂₈ N ₂ O ₇
297463	1-Me-2(S)-pyrrolidinyl-CH2	3-Pyr	2HCl	C ₃₁ H ₃₃ N ₃ O ₆ .2HCl
297464	CH2Ph	4-Pip-O	HCl	C ₃₂ H ₃₄ N ₂ O ₇ .HCl
297466	2-Pyr-CH2	4-(1,3-dioxo-2-isoindolinyl)-PhCONHCH2		C ₄₂ H ₃₄ N ₄ O ₉

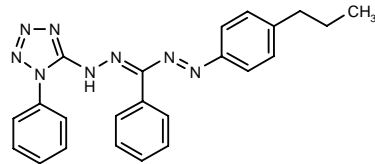
SOURCE – Tanabe Seiyaku.

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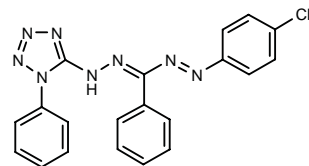
297665

1-(4-Propylphenyl)-3-phenyl-5-(1-phenyl-1 H-tetrazol-5-yl)formazan



C23 H22 N8; Mol wt: 410.4828

ACTION – Endothelin-converting enzyme (ECE) inhibitor (IC₅₀ = 2.6 μM against ECE from rat lung) that is potentially useful for the treatment or prevention of cardiovascular disorders such as hypertension and atherosclerosis. Another exemplified hydrazone derivative is:



297668: C20 H15 Cl N8

SOURCE – Sumitomo Pharmaceuticals.

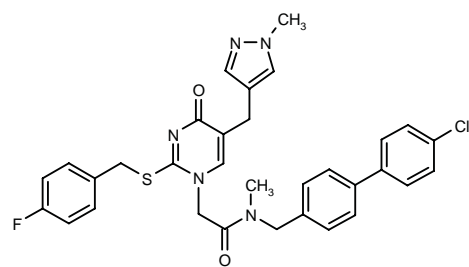
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

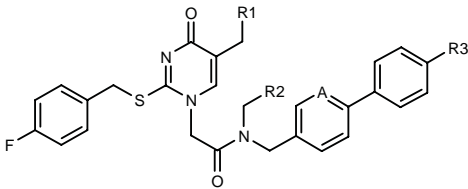
296831

N-(4'-Chlorobiphenyl-4-ylmethyl)-2-[2-(4-fluorobenzyl-sulfanyl)-5-(1-methyl-1 H-pyrazol-4-ylmethyl)-1,4-dihydro-4-oxypyrimidin-1-yl]-N-methylacetamide



C32 H29 Cl F N5 O2 S; Mol wt: 602.1311

ACTION – Potent inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂), particularly useful for the treatment of atherosclerosis. Other specifically claimed pyrimidinone derivatives are:



Compound	R1	R2	R3	A	Formula
296832	1-Me-4-pyrazolyl	H	CF3	CH	C ₃₃ H ₂₉ F ₄ N ₅ O ₂ S
296833	1-Me-4-pyrazolyl	CH2N(Me)2	Cl	CH	C ₃₅ H ₃₆ ClFN ₆ O ₂ S
296834	2-(4-morpholinyl)-5-pyrimidinyl	H	Cl	CH	C ₃₆ H ₃₄ ClFN ₆ O ₃ S
296835	1-Me-4-pyrazolyl	CH2N(Me)2	CF3	CH	C ₃₆ H ₃₆ F ₄ N ₆ O ₂ S
296836	1-Me-4-pyrazolyl	CH2N(Et)2	Cl	CH	C ₃₇ H ₄₀ ClFN ₆ O ₂ S
296837	1-Me-4-pyrazolyl	CH2N(Et)2	CF3	N	C ₃₇ H ₃₉ F ₄ N ₇ O ₂ S
296838	1-Me-4-pyrazolyl	1-Pip-CH2	CF3	CH	C ₄₇ H ₅₂ F ₄ N ₆ O ₁₄ S
296839	1-Me-4-pyrazolyl	CO2Na	CF3	CH	C ₃₄ H ₂₈ F ₄ N ₅ NaO ₄ S
296840	1-Me-4-pyrazolyl	CH2N(Et)2	CF3	CH	C ₃₈ H ₄₀ F ₄ N ₆ O ₂ S

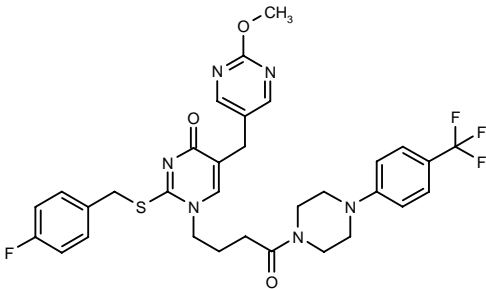
SOURCE – GlaxoSmithKline.

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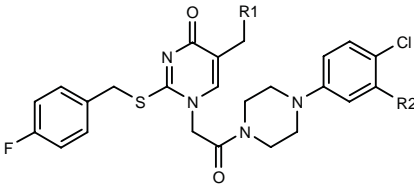
296841

2-(4-Fluorobenzylsulfanyl)-5-(2-methoxypyrimidin-5-yl-methyl)-1-[4-oxo-4-[4-[4-(trifluoromethyl)phenyl]piperazin-1-yl]butyl]pyrimidin-4(1*H*)-one



C32 H32 F4 N6 O3 S; Mol wt: 656.7018

ACTION – Potent inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂; IC₅₀ = 2 nM), particularly useful for the treatment of atherosclerosis. Other specifically claimed pyrimidinone derivatives are:



Compound	R1	R2	Formula
296842	2-MeO-5-pyrimidinyl	Cl	C ₂₉ H ₂₇ Cl ₂ FN ₆ O ₃ S
296843	2-MeO-5-pyrimidinyl	H	C ₂₉ H ₂₈ ClFN ₆ O ₃ S
296844	1-Me-4-pyrazolyl	Cl	C ₂₈ H ₂₇ Cl ₂ FN ₆ O ₂ S

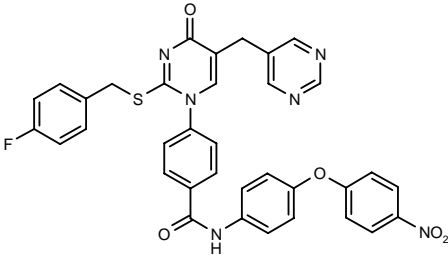
SOURCE – GlaxoSmithKline.

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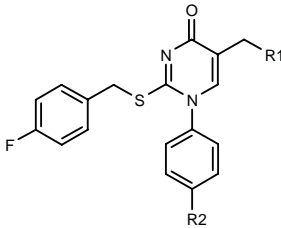
297085

4-[2-(4-Fluorobenzylsulfanyl)-4-oxo-5-(5-pyrimidinyl-methyl)-1,4-dihydropyrimidin-1-yl]-*N*-[4-(4-nitrophenoxy)-phenyl]benzamide



C35 H25 F N6 O5 S; Mol wt: 660.6835

ACTION – Agent for the treatment of atherosclerosis, a potent inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂), as demonstrated by an IC₅₀ in the range of 10-40 nM when tested *in vitro* against recombinant Lp-PLA₂. Other exemplified compounds from this series of pyrimidinone derivatives include the following:



Compound	R1	R2	Formula
297086	5-pyrimidinyl	4-(4-CF3O-PhO)-Ph-NHCO	C ₃₆ H ₂₅ F ₄ N ₅ O ₄ S
297087	5-pyrimidinyl	CON(CH2Ph)C7H15	C ₃₇ H ₃₈ FN ₅ O ₂ S
297088	2-EtO-5-pyrimidinyl	CON(CH2Ph)C7H15	C ₃₉ H ₄₂ FN ₅ O ₃ S
297089	2-EtO-5-pyrimidinyl	4-(4-CF3O-PhO)-Ph-NHCO	C ₃₈ H ₂₉ F ₄ N ₅ O ₅ S
297090	2-oxo-1,2-dihydro-5-pyrimidinyl	CON(CH2Ph)C7H15	C ₃₇ H ₃₈ FN ₅ O ₃ S
297092	2-oxo-1,2-dihydro-5-pyrimidinyl	4-(4-CF3O-PhO)-Ph-NHCO	C ₃₆ H ₂₅ F ₄ N ₅ O ₅ S
297094	1-(CH2CO2H)-2-oxo-1,2-dihydro-5-pyrimidinyl	CON(CH2Ph)C7H15	C ₃₉ H ₄₀ FN ₅ O ₅ S
297095	1-(CH2CO2H)-2-oxo-1,2-dihydro-5-pyrimidinyl	4-(4-CF3O-PhO)-Ph-NHCO	C ₃₈ H ₂₇ F ₄ N ₅ O ₇ S
297096	5-pyrimidinyl	4-F-PhCH2-N(Me)SO2CH2	C ₃₁ H ₂₇ F ₂ N ₅ O ₃ S ₂

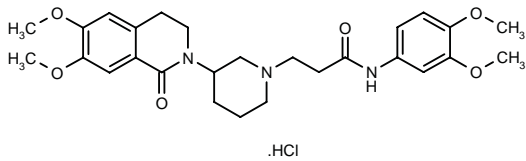
SOURCE – GlaxoSmithKline.

REFERENCES

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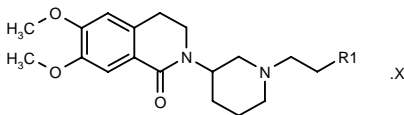
297765

3-[3-(6,7-Dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)piperidin-1-yl]-N-(3,4-dimethoxyphenyl)propionamide hydrochloride



C27 H35 N3 O6 . HCl; Mol wt: 534.0494

ACTION – Agent for the treatment of cardiovascular disorders such as angina pectoris, myocardial infarction, congestive heart failure and arrhythmia that acts as an I_f current inhibitor and bradycardic agent. Other exemplified compounds from this series of 1-oxo-1,2,3,4-tetrahydroisoquinoline derivatives include the following:



Compound	R1	X	Formula
297766	3-MeO-PhNHCO	HCl	C ₂₆ H ₃₃ N ₃ O ₅ .HCl
297767	4-CN-PhNHCO	oxalate	C ₂₆ H ₃₀ N ₄ O ₄ .C ₂ H ₂ O ₄
297768	2-Me-4-MeO-PhNHCO	oxalate	C ₂₇ H ₃₅ N ₃ O ₅ .C ₂ H ₂ O ₄
297769	3,4-(EtO)2-PhNHCO	HCl	C ₂₉ H ₃₉ N ₃ O ₆ .HCl
297770	3,4,5-(MeO)2-PhNHCO	HCl	C ₂₈ H ₃₇ N ₃ O ₇ .HCl
297771	3-(MeSO2)-PhNHCO	HCl	C ₂₆ H ₃₃ N ₃ O ₆ S.HCl
297772	6-quinolyl-NHCO	2HCl	C ₂₈ H ₃₂ N ₄ O ₄ .2HCl
297773	3,4-(MeO)2-PhNHCOCH2	oxalate	C ₂₈ H ₃₇ N ₃ O ₆ .C ₂ H ₂ O ₄

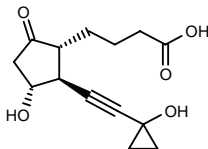
SOURCE – Yamanouchi.

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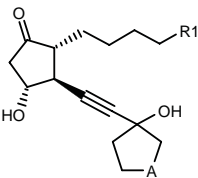
297782

4-[(1*R*,2*S*,3*R*)-3-Hydroxy-2-[2-(1-hydroxycyclopropyl)-ethynyl]-5-oxocyclopentyl]butyric acid



C14 H18 O5; Mol wt: 266.2912

ACTION – An inhibitor of vascular smooth muscle proliferation, with potential for the treatment of vascular hypertrophy and obstruction and as a preventive for post-PTCA restenosis. Other exemplified compounds from this series of prostaglandin E₁ (PGE₁) derivatives include the following:



Compound	R1	A	Formula
297783	CH2CH2CO2H	-(CH2)4-	C ₂₂ H ₃₄ O ₅
297784	CH=CHCO2H	-(CH2)3-	C ₂₁ H ₃₀ O ₅
297785	ethynylene-CO2H	-(CH2)-	C ₁₉ H ₂₄ O ₅
297786	OCH2CO2Me	-(CH2)3-	C ₂₁ H ₃₂ O ₆
297787	SCH2CO2H	-(CH2)3-	C ₂₀ H ₃₀ O ₅ S

SOURCE – Taisho.

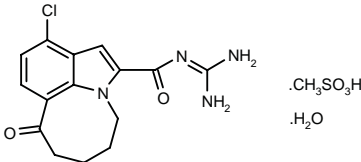
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SMP-300

280658

N-(11-Chloro-8-oxo-5,6,7,8-tetrahydro-4*H*-azocino-[3,2,1-*h*]indol-2-ylcarbonyl)guanidine methanesulfonate hydrate



C15 H15 Cl N4 O2 . C H4 O3 S . H2O; Mol wt: 432.8829

ACTION – Na⁺/H⁺ exchange inhibitor proven able to inhibit recovery from acidosis in rat myocytes (IC₅₀ = 6 nM), whereas it was inactive at up to 1 μM on Na⁺/Ca⁺ exchange in rat myocardium and showed no affinity at Ca²⁺ or K⁺ channels and other channels or receptors at concentrations up to 10 μM. In isolated perfused rat hearts subjected to ischemia and reperfusion, compound given before ischemia significantly improved postischemic recovery of cardiac function. In anesthetized rats, doses of 0.03-0.3 mg/kg i.v. prevented isoproterenol-induced S-T segment depression and a dose of 0.1 μg/kg i.v. prevented S-T segment depression induced by vasopressin. Compound at the dose of 0.3 mg/kg i.v. had no significant effect on normal hemodynamics. In a chronic ischemia model in rats subjected to left coronary artery ligation, compound at a dose of 20 mg/kg/day p.o. for 12 weeks suppressed left ventricular remodeling caused by heart stenosis. Potentially useful as an antianginal agent.

SOURCE – Sumitomo Pharmaceuticals.

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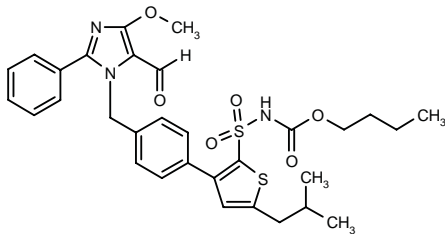
6. Watanabe, K. et al. *Inhibition of Na⁺/H⁺ exchange attenuates left ventricular remodeling in rat coronary stenosis model.* J Mol Cell Cardiol 2000, 32(11): Abst 37.

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HEART FAILURE THERAPY

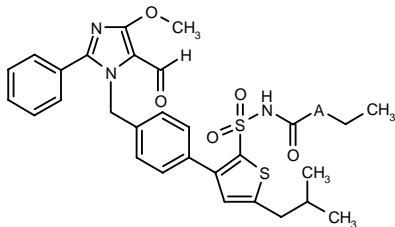
297047

N-[3-[4-(5-Formyl-4-methoxy-2-phenyl-1*H*-imidazol-1-ylmethyl)phenyl]-5-isobutylthien-2-ylsulfonyl]carbamic acid butyl ester



C31 H35 N3 O6 S2; Mol wt: 609.7645

ACTION – Potent agonist of angiotensin(1-7) receptors in endothelial cells that thus stimulates the production and release of cGMP and nitric oxide and is potentially useful for the treatment of hypertension, heart hypertrophy, heart failure, angina pectoris, myocardial infarction, vascular restenosis following angioplasty, cardiomyopathy and endothelial dysfunction. The compound demonstrated high affinity (IC₅₀ = 30 nM) and agonist activity (EC₅₀ = 0.3 μM) for angiotensin(1-7) receptors in endothelial cells. It also showed cardioprotective properties in isolated rat hearts and significant antithrombotic activity in human platelet-rich plasma. Other exemplified 1-(4-thienyl-benzyl)imidazoles include the following:



Compound	A	Formula
297049	O	C ₂₉ H ₃₁ N ₃ O ₆ S ₂
297050	NH	C ₂₉ H ₃₂ N ₄ O ₅ S ₂

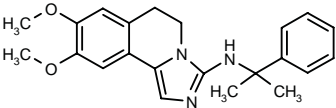
SOURCE – Aventis Pharma.

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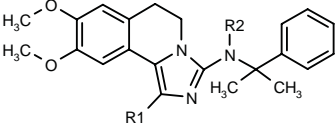
297789

8,9-Dimethoxy-N-(1-methyl-1-phenylethyl)-5,6-dihydro-imidazo[5,1-a]isoquinolin-3-amine



C22 H25 N3 O2; Mol wt: 363.4585

ACTION – A representative imidazo-containing heterocyclic compound with potential for the treatment or prevention of congestive heart failure, arrhythmia, hypotension, cardiac reperfusion injury, arteriosclerosis, restenosis, bacterial infection, cancer, Kaposi's sarcoma, psoriasis, migraine, nasal congestion, allergic responses, rheumatoid arthritis and osteoporosis. Other exemplified compounds are:



Compound	R1	R2	Formula
297790	H	Me	C ₂₃ H ₂₇ N ₃ O ₂
297791	Ph	H	C ₂₈ H ₂₉ N ₃ O ₂

SOURCE – Procter & Gamble.

REFERENCES

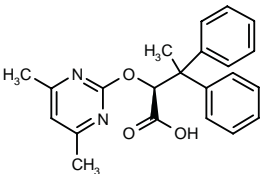
1. Liu, S. et al. (The Procter & Gamble Co.) *Imidazo-containing heterocyclic cpds., their compsns. and uses.* WO 0069860.

BSF-302146*

258655

(+)-2(S)-(4,6-Dimethylpyrimidin-2-yloxy)-3,3-diphenyl-butyric acid

LU-302146



C22 H22 N2 O3; Mol wt: 362.4268

ACTION – Endothelin receptor antagonist with 100-fold selectivity for ET_A versus ET_B receptors, able to inhibit the big ET-induced increase in blood pressure in rats at 10 mg/kg p.o. In rats with secondary biliary fibrosis, compound given at the dose of 10 mg/kg/day for 6 weeks reduced hepatic collagen content. Moreover, it was found to be active in inhibiting porcine vein graft thickening when given at the oral dose of 30 mg/kg/day for 30 days to pigs with saphenous vein–carotid artery interpositional grafting. In this model, BSF-302146 markedly reduced medial and intimal thickening and strongly increased luminal area in vein grafts compared to untreated controls, indicating possible beneficial effects in the treatment of late vein graft failure in man. Compound was also seen to inhibit the *in vivo* growth, dissemination and ascites production of human pancreatic cancer PaCa cells, as well as to improve endothelium-dependent vasodilatory responses to natriuretic peptides in experimental atherosclerosis in rabbits. Compound is undergoing phase I clinical trials for the treatment of congestive heart failure.

SOURCES – Knoll (Abbott).

REFERENCES

1. Klinge, D. et al. (BASF AG) *Novel α -hydroxylic acid derivs., their production and use*. DE 19614533, EP 0892787, JP 2000508326, WO 9738981.
2. Bulbulia, R.A. et al. *The endothelin A (ETA) receptor antagonist, BSF 302146, is a potent inhibitor of porcine vein graft thickening, in vivo*. Br J Pharmacol 2000, 131(Suppl.): Abst 31P.
3. Cho, J.J. et al. *Specific endothelin A receptor antagonism retards fibrogenesis in rat biliary fibrosis*. 35th Annu Meet Eur Assoc Study Liver (April 29-May 3, Rotterdam) 2000, Abst P/C02/19.
4. Hotz, H.G. et al. *The effect of selective endothelin-A-receptor blockade on human pancreatic cancer in-vivo*. Pancreas 2000, 21(4): 448.
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8. Weber, A. et al. *Functional in vitro investigations and in vivo evaluation of the endothelin system in porcine detrusor: The role of selective pharmacological endothelin-antagonists*. J Urol 1999, 161(4, Suppl.): 48.
9. Willi, A. et al. *LU 208075 and LU 302146, two novel ETa-selective endothelin receptor antagonists: S.A.R. of 3,3 diaryl propionic acid derivatives*. 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst 020.
10. Wolf, S.C. et al. *Endothelin-receptor antagonists in uremic cardiomyopathy*. J Cardiovasc Pharmacol 2000, 36(5, Suppl. 1): S348.
11. *Abbott Laboratories*. Merrill Lynch Global Healthcare Conf (Feb 6-8, New York) 2001.

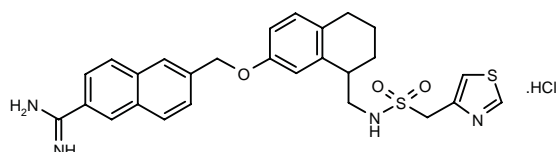
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

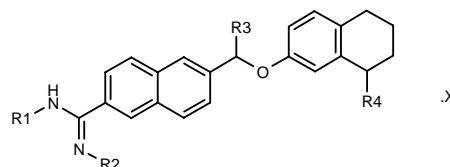
296649

6-[8-(4-Thiazolylmethylsulfonamidomethyl)-5,6,7,8-tetrahydronaphthalen-2-yloxymethyl]naphthalene-2-carboxamide hydrochloride

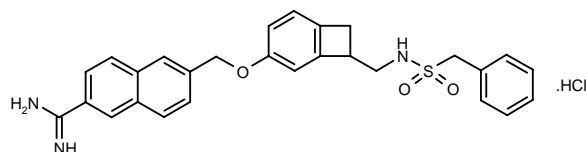


C27 H28 N4 O3 S2 . HCl; Mol wt: 557.1361

ACTION – Anticoagulant and antithrombotic agent with factor VII/VIIa-inhibitory activity. A representative compound from a series of 6-[[*(aryl and heteroaryl)oxy*]-methyl]naphthalene-2-carboximidamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	X	Formula
296651	H	H	H	3-MeO-PhCH2CONH		C ₃₁ H ₃₁ N ₃ O ₃
296652	H	H	H	3-Pyr-CH2NHCONH		C ₂₉ H ₂₉ N ₅ O ₂
296653	H	H	H	3-MeO-PhCH2-SO2NHCH2		C ₃₁ H ₃₃ N ₃ O ₄ S
296654	H	H	H	NHCOCH2Ph	HCl	C ₃₀ H ₂₉ N ₃ O ₂ .HCl
296655	H	H	CO2H	3-MeO-PhCH2-SO2NHCH2		C ₃₂ H ₃₃ N ₃ O ₆ S
296656	H	H	H	3-CO2H-PhCH2-SO2NHCH2	HCl	C ₃₁ H ₃₁ N ₃ O ₅ S.HCl
296659	H	H	H	3-MeO-PhC(=NH)-NHCH2NH	HCl	C ₃₁ H ₃₃ N ₅ O ₂ .HCl
296663	CO2Et	H	H	3-CO2Me-Ph-CH2NHCONH	HCl	C ₃₆ H ₃₆ N ₄ O ₆ .HCl
296665	H	OH	H	3-CO2Me-Ph-CH2SO2NHCH2	HCl	C ₃₂ H ₃₃ N ₃ O ₆ S.HCl



296662: C28 H27 N3 O3 S . HCl

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Alcouffe, C. et al. (Sanofi-Synthélabo) *6-[[*(Aryl and heteroaryl)oxy*]-methyl]-naphthalene-2-carboximidamide derivs., preparation and therapeutic application thereof*. FR 2793247, WO 0066545.

ACTION – Endothelin receptor antagonist with 100-fold selectivity for ET_A versus ET_B receptors, able to inhibit the big ET-induced increase in blood pressure in rats at 10 mg/kg p.o. In rats with secondary biliary fibrosis, compound given at the dose of 10 mg/kg/day for 6 weeks reduced hepatic collagen content. Moreover, it was found to be active in inhibiting porcine vein graft thickening when given at the oral dose of 30 mg/kg/day for 30 days to pigs with saphenous vein–carotid artery interpositional grafting. In this model, BSF-302146 markedly reduced medial and intimal thickening and strongly increased luminal area in vein grafts compared to untreated controls, indicating possible beneficial effects in the treatment of late vein graft failure in man. Compound was also seen to inhibit the *in vivo* growth, dissemination and ascites production of human pancreatic cancer PaCa cells, as well as to improve endothelium-dependent vasodilatory responses to natriuretic peptides in experimental atherosclerosis in rabbits. Compound is undergoing phase I clinical trials for the treatment of congestive heart failure.

SOURCES – Knoll (Abbott).

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2. Bulbulia, R.A. et al. *The endothelin A (ETA) receptor antagonist, BSF 302146, is a potent inhibitor of porcine vein graft thickening, in vivo*. Br J Pharmacol 2000, 131(Suppl.): Abst 31P.
3. Cho, J.J. et al. *Specific endothelin A receptor antagonism retards fibrogenesis in rat biliary fibrosis*. 35th Annu Meet Eur Assoc Study Liver (April 29-May 3, Rotterdam) 2000, Abst P/C02/19.
4. Hotz, H.G. et al. *The effect of selective endothelin-A-receptor blockade on human pancreatic cancer in-vivo*. Pancreas 2000, 21(4): 448.
5. Jansen, R. et al. *Structural similarity and its supprises: Endothelin receptor antagonists - Process research and development report*. Org Process Res Dev 2001, 5(1): 16.
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8. Weber, A. et al. *Functional in vitro investigations and in vivo evaluation of the endothelin system in porcine detrusor: The role of selective pharmacological endothelin-antagonists*. J Urol 1999, 161(4, Suppl.): 48.
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10. Wolf, S.C. et al. *Endothelin-receptor antagonists in uremic cardiomyopathy*. J Cardiovasc Pharmacol 2000, 36(5, Suppl. 1): S348.
11. *Abbott Laboratories*. Merrill Lynch Global Healthcare Conf (Feb 6-8, New York) 2001.

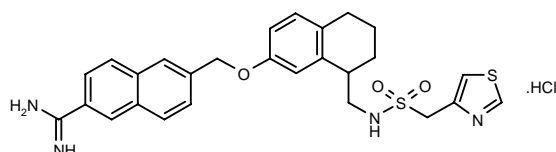
*Identified compound **258655** (see **257246**) Drug Data Rep 1998, 020(02): 0130.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

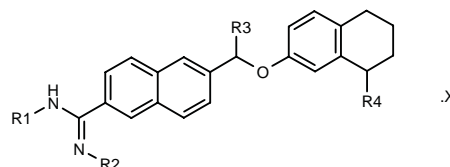
296649

6-[8-(4-Thiazolylmethylsulfonamidomethyl)-5,6,7,8-tetrahydronaphthalen-2-yloxymethyl]naphthalene-2-carboxamide hydrochloride

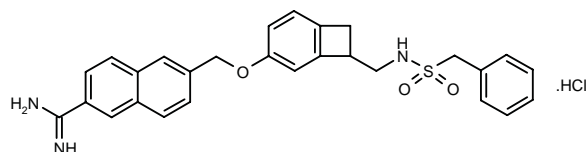


C27 H28 N4 O3 S2 . HCl; Mol wt: 557.1361

ACTION – Anticoagulant and antithrombotic agent with factor VII/VIIa-inhibitory activity. A representative compound from a series of 6-[[*(aryl and heteroaryl)oxy*]-methyl]naphthalene-2-carboximidamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	X	Formula
296651	H	H	H	3-MeO-PhCH2CONH		C ₃₁ H ₃₁ N ₃ O ₃
296652	H	H	H	3-Pyr-CH2NHCONH		C ₂₉ H ₂₉ N ₅ O ₂
296653	H	H	H	3-MeO-PhCH2-SO2NHCH2		C ₃₁ H ₃₃ N ₃ O ₄ S
296654	H	H	H	NHCOCH2Ph	HCl	C ₃₀ H ₂₉ N ₃ O ₂ .HCl
296655	H	H	CO2H	3-MeO-PhCH2-SO2NHCH2		C ₃₂ H ₃₃ N ₃ O ₆ S
296656	H	H	H	3-CO2H-PhCH2-SO2NHCH2	HCl	C ₃₁ H ₃₁ N ₃ O ₅ S.HCl
296659	H	H	H	3-MeO-PhC(=NH)-NHCH2NH	HCl	C ₃₁ H ₃₃ N ₅ O ₂ .HCl
296663	CO2Et	H	H	3-CO2Me-Ph-CH2NHCONH	HCl	C ₃₆ H ₃₆ N ₄ O ₆ .HCl
296665	H	OH	H	3-CO2Me-Ph-CH2SO2NHCH2	HCl	C ₃₂ H ₃₃ N ₃ O ₆ S.HCl



296662: C28 H27 N3 O3 S . HCl

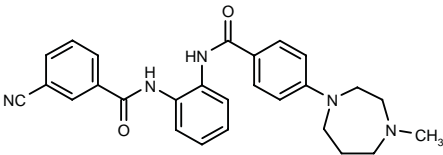
SOURCE – Sanofi-Synthélabo.

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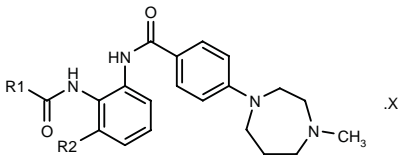
297774

3-Cyano-*N*-[2-[4-(4-methylperhydro-1,4-diazepin-1-yl)-benzamido]phenyl]benzamide



C27 H27 N5 O2; Mol wt: 453.5433

ACTION – Anticoagulant and antithrombotic agent with factor Xa-inhibitory activity. Other exemplified compounds from this series of diazepane derivatives include the following:



Compound	R1	R2	X	Formula
297775	3-Me-Ph	H	HCl	C ₂₇ H ₃₀ N ₄ O ₂ ·HCl
297776	4-MeO-Ph	Me	HCl	C ₂₈ H ₃₂ N ₄ O ₃ ·HCl
297777	2-Br-5-MeO-Ph	H		C ₂₇ H ₂₉ BrN ₄ O ₃
297778	3-I-Ph	H		C ₂₆ H ₂₇ IN ₄ O ₂
297779	4,5-(Me)2-2-furyl	H		C ₂₆ H ₃₀ N ₄ O ₃
297780	5,6-(Cl)2-3-Pyr	H		C ₂₅ H ₂₅ Cl ₂ N ₅ O ₂
297781	6-indolyl	H		C ₂₈ H ₂₉ N ₅ O ₂

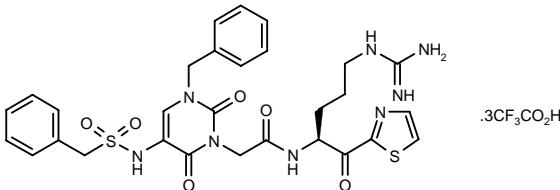
SOURCE – Yamanouchi.

REFERENCES

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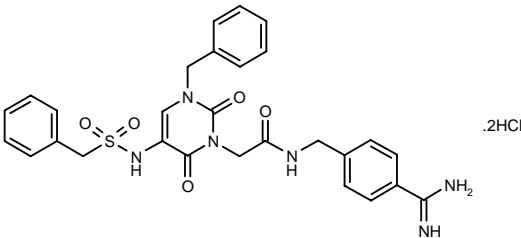
297832

2-[3-Benzyl-5-(benzylsulfonamido)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl]-*N*-[4-guanidino-1(*S*)-(2-thiazolylcarbonyl)butyl]acetamide tris(trifluoroacetate)



C29 H32 N8 O6 S2 . 3 C2 H F3 O2; Mol wt: 994.8195

ACTION – Anticoagulant and antithrombotic agent for the treatment or prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular diseases, an inhibitor of serine proteases of the coagulation cascade such as tissue factor/factor VIIa (IC₅₀ = 12.9 μM; human), thrombin (IC₅₀ = 0.3 μM; human), factor Xa (IC₅₀ = 0.2 μM; human) and trypsin (IC₅₀ = 0.2 μM; porcine). Another compound from this series of substituted polycyclic aryl and heteroaryl uracils is:



297833: C28 H28 N6 O5 S . 2HCl

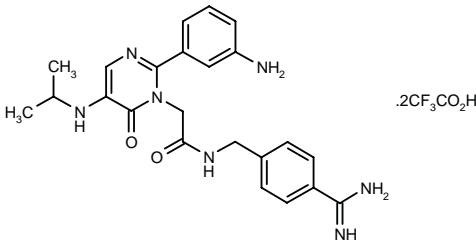
SOURCE – Pharmacia.

REFERENCES

1. South, M.S. et al. (Pharmacia Corp.) *Substd. polycyclic aryl and heteroaryl uracils as anticoagulative agents*. WO 0069833.

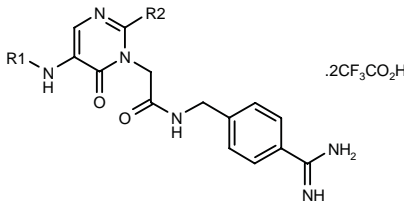
297836

N-(4-Amidinobenzyl)-2-[2-(3-aminophenyl)-5-(isopropyl-amino)-6-oxo-1,6-dihydropyrimidin-1-yl]acetamide bis-(trifluoroacetate)



C23 H27 N7 O2 . 2 C2 H F3 O2; Mol wt: 661.5571

ACTION – Anticoagulant and antithrombotic agent for the treatment or prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular diseases, an inhibitor of serine proteases of the coagulation cascade such as tissue factor/factor VIIa (IC₅₀ = 0.05 μM; human), thrombin (43% inhibition at 30 μM; human), factor Xa (33% inhibition at 30 μM; human) and trypsin (IC₅₀ < 0.04 μM; porcine). Other compounds from this series of substituted polycyclic aryl and heteroaryl pyrimidinones include the following:



Compound	R1	R2	Formula
297838	i-Pr	3-Pyr	C ₂₂ H ₂₆ N ₇ O ₂ ·2C ₂ HF ₃ O ₂
297840	cyclobutyl	3-NH2-Ph	C ₂₄ H ₂₇ N ₇ O ₂ ·2C ₂ HF ₃ O ₂

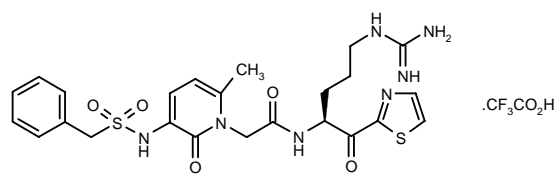
SOURCE – Pharmacia.

REFERENCES

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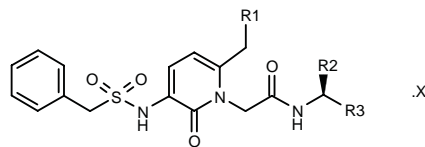
297841

2-[3-(Benzylsulfonamido)-6-methyl-2-oxo-1,2-dihydro-pyridin-1-yl]-N-[4-guanidino-1(S)-(2-thiazolylcarbonyl)-butyl]acetamide trifluoroacetate

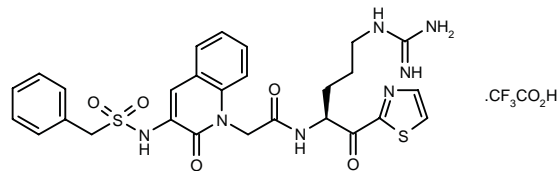


C24 H29 N7 O5 S2 . C2 H F3 O2; Mol wt: 673.6910

ACTION – Anticoagulant and antithrombotic agent for the treatment or prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular diseases, an inhibitor of serine proteases of the coagulation cascade such as tissue factor/factor VIIa (IC₅₀ = 0.8 μM; human), thrombin (IC₅₀ < 0.04 μM; human), factor Xa (IC₅₀ < 4.0 μM; human) and trypsin (IC₅₀ = 0.2 μM; porcine). Other compounds from this series of substituted polycyclic aryl and heteroaryl pyridones include the following:



Compound	R1	R2	R3	X	Formula
297844	CH2Ph	(CH2)3NH-C(=NH)NH2	2-thiazolyl-CO	CF3CO2H	C ₃₁ H ₃₅ N ₇ O ₅ S ₂ .C ₂ HF ₃ O ₂
297845	CH2Ph	H	4-[NH2C(=NH)]-Ph	tosylate	C ₃₀ H ₃₁ N ₅ O ₄ S .C ₇ H ₈ O ₃ S
297846	H	H	4-[NH2C(=NH)]-Ph	tosylate	C ₂₃ H ₂₅ N ₅ O ₄ S .C ₇ H ₈ O ₃ S
297847	CH2Ph	H	1-[C(=NH)NH2]-4-Pip	HCl	C ₂₉ H ₃₆ N ₆ O ₄ S .HCl



297843: C27 H29 N7 O5 S2 . C2 H F3 O2

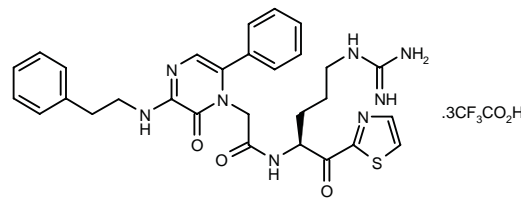
SOURCE – Pharmacia.

REFERENCES

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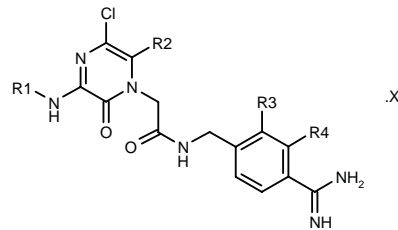
297848

N-[4-Guanidino-1(S)-(2-thiazolylcarbonyl)butyl]-2-[2-oxo-6-phenyl-3-(2-phenylethylamino)-1,2-dihdropyrazin-1-yl]acetamide tris(trifluoroacetate)

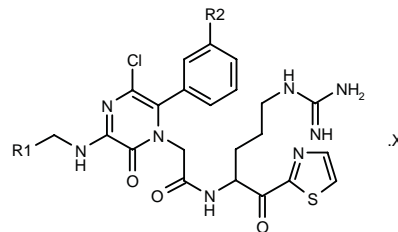


C29 H32 N8 O3 S . 3 C2 H F3 O2; Mol wt: 914.7565

ACTION – Anticoagulant and antithrombotic agent for the treatment or prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular diseases, an inhibitor of serine proteases of the coagulation cascade such as tissue factor/factor VIIa (IC₅₀ = 0.1 μM; human), thrombin (IC₅₀ < 0.04 μM; human), factor Xa (IC₅₀ = 1 μM; human) and trypsin (IC₅₀ = 0.4 μM; porcine). Other compounds from this series of substituted polycyclic aryl and heteroaryl pyrazinones include the following:



Compound	R1	R2	R3	R4	X	Formula
297850	cyclobutyl	3-NH2-Ph	H	F		C ₂₄ H ₂₅ ClFN ₇ O ₂
297851	cyclobutyl	3-NH2-Ph	F	H		C ₂₄ H ₂₅ ClFN ₇ O ₂
297852	CH2CH2Ph	Ph	H	H		C ₂₈ H ₂₇ ClN ₆ O ₂
297853	cyclobutyl	5-NH2-2-thienyl	H	H	CF3CO2H	C ₂₂ H ₂₄ ClN ₇ O ₂ S .C ₂ HF ₃ O ₂
297854	i-Pr	2-F-5-NH2-Ph	F	H		C ₂₃ H ₂₄ ClF ₂ N ₇ O ₂
297857	cyclopropyl	3-NH2-Ph	F	H		C ₂₃ H ₂₃ ClFN ₇ O ₂
297858	i-Pr	3-NH2-Ph	F	H		C ₂₃ H ₂₅ ClFN ₇ O ₂



Compound	R1	R2	X	Formula
297849	CH2Ph	H	3CF3CO2H	C ₂₉ H ₃₁ ClN ₈ O ₃ S.3C ₂ HF ₃ O ₂
297855	Ph	NH2		C ₂₈ H ₃₀ ClN ₉ O ₃ S

SOURCE – Pharmacia.

REFERENCES

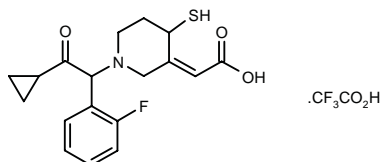
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ANTIPLATELET THERAPY

R-99224

299858

(2Z)-[1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidin-3-ylidene]ethanoic acid trifluoroacetate



C18 H20 F N O3 S . C2 H F3 O2; Mol wt: 463.4459

ACTION – Active hepatic metabolite of the platelet ADP receptor antagonist CS-747⁺, a selective and irreversible antagonist of G_i-linked P2T receptors, as demonstrated by complete inhibition of [³H]-2-MeS-ADP binding obtained with compound in the presence of the selective P2Y₁ antagonist A3P5PS. In addition, R-99224 inhibited ADP-induced [¹²⁵I]-fibrinogen binding to human platelets in a concentration-dependent manner and the ADP-induced decrease in cAMP levels in PGE₁-stimulated platelets. Compound is a potent inhibitor of ADP (3 μM)-induced platelet aggregation *in vitro* (IC₅₀ = 0.11 and 0.42 μM, respectively, in human and rat platelets) and *ex vivo* in rats (ED₅₀ = 0.48 mg/kg i.v.). CS-747, inactive or weakly active *in vitro*, inhibited ADP-induced rat platelet aggregation after oral administration of 1 and 3 mg/kg, and the effect was long lasting (up to 72 h postdose), and dose-dependent reductions in thrombus formation were seen in the rat arteriovenous shunt model (ED₅₀ = 0.68 mg/kg p.o.).

SOURCES – Sankyo; Ube.

REFERENCES

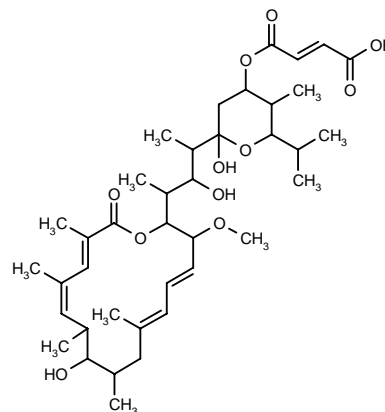
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- Sugidachi, A. et al. *The in vivo pharmacological profile of CS-747, a novel antiplatelet agent with platelet ADP receptor antagonist properties.* Br J Pharmacol 2000, 129(7): 1439.

*Drug Data Rep 1999, 021(04): 0323.

TS-155-2

297664

18-[4-(3-Carboxy-2-propenoyloxy)-2-hydroxy-6-isopropyl-5-methyltetrahydropyran-2-yl]-7,17-dihydroxy-14-methoxy-2,4,6,8,10,16-hexamethyl-2,4,10,12-nonadeca-tetraeno-15-lactone



C39 H60 O11; Mol wt: 704.8920

ACTION – A compound isolated from *Streptomyces* sp. TS7155 (FERM P-17212), that was found to inhibit thrombin-induced Ca²⁺ entry into cells and is thus expected to be useful as an antiplatelet and anti-hypertensive agent, as well as for the treatment of cerebral ischemic disorders and chronic rheumatoid arthritis.

SOURCE – Teijin.

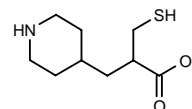
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THROMBOLYTICS

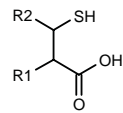
296845

3-(4-Piperidiny)-2-(sulfanylmethyl)propionic acid



C9 H17 N O2 S; Mol wt: 203.3043

ACTION – Carboxypeptidase U (CPU) inhibitor that is expected to facilitate fibrinolysis and is thus useful for the treatment or prophylaxis of thrombosis and hypercoagulability. Other exemplified compounds include the following:



Compound	R1	R2	Formula
296846	2-NH2-4-Pyr-CH2	H	C ₉ H ₁₂ N ₂ O ₂ S
296847	4-Pip-CONH	H	C ₉ H ₁₆ N ₂ O ₃ S
296848	6-NH2-4-Me-3-Pyr-CH2	H	C ₁₀ H ₁₄ N ₂ O ₂ S
296849	6-NH2-3-Pyr-CH2	Me	C ₁₀ H ₁₄ N ₂ O ₂ S
296850	cis-4-NH2-2-cyclopenten-1-yl-CH2	H	C ₉ H ₁₅ NO ₂ S
296851	6-NH2-3-Pyr-CH(CH2Ph)	H	C ₁₆ H ₁₈ N ₂ O ₂ S
296852	2-NH2-5-thiazolyl-CH2	H	C ₇ H ₁₀ N ₂ O ₂ S ₂

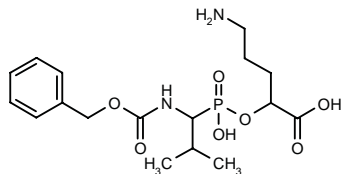
SOURCE – AstraZeneca.

REFERENCES

1. Linschoten, M. et al. (AstraZeneca AB) *New cpds.* WO 0066557.

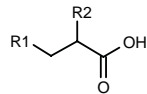
296853

5-Amino-2-[1-(benzyloxycarbonylamino)-2-methylpropyl-(hydroxy)phosphoryloxy]pentanoic acid



C17 H27 N2 O7 P; Mol wt: 402.3813

ACTION – Carboxypeptidase U (CPU) inhibitor that is expected to facilitate fibrinolysis and is thus useful for the treatment or prophylaxis of thrombosis and hyper-coagulability. Other exemplified compounds include the following:



Compound	R1	R2	Formula
296854	4-Pip-CH2	CONHOH	C ₁₀ H ₁₈ N ₂ O ₄
296855	1-(t-BuOCO)-3-Pip	CO2H	C ₁₄ H ₂₃ NO ₆
296856	3-NH2-cyclohexyl	CH2CO2H	C ₁₁ H ₁₉ NO ₄
296857	6-NH2-3-Pyr	CH(CO2H)Bu	C ₁₄ H ₂₀ N ₂ O ₄

SOURCE – AstraZeneca.

REFERENCES

1. Linschoten, M. and Polla, M. (AstraZeneca AB) *New cpds.* WO 0066550.

FKK-138

291545

Modified recombinant tissue-type plasminogen activator (tPA) produced in Escherichia coli; a single-stranded protein in which the region from the N-terminus to the kringle 1 domain of human native tPA is deleted and Arg at position 275 is replaced by Asp

ACTION – Thrombolytic agent, a modified recombinant human tissue-type plasminogen activator (tPA) which, like alteplase, shows concentration-dependent binding to human fibrin clot, with about 75% of the binding affinity of alteplase. In two canine models of coronary artery thrombosis induced by copper coil or by endothelial cell injury, it produced dose-dependent and significant thrombolysis, but unlike alteplase, it was not associated with acute reocclusion after reperfusion. In a phase I study in healthy male volunteers, compound as single i.v. bolus doses of 0.25, 0.5, 1, 2, 4 and 6 mg was well tolerated and pharmacokinetics (AUC and C_{max}) increased in a dose-dependent fashion, with a mean elimination half-life of about 17 min. In another clinical trial, the efficacy and safety of single i.v. doses of compound were examined in patients with acute myocardial infarction and a completely obstructed coronary artery. A dose-dependent response was observed at doses of 0.1, 0.2 and 0.3 mg/kg and a high recanalization rate (70%) was seen 30 min after the highest dose. No serious adverse events such as cerebral hemorrhage or hemorrhagic shock were observed.

SOURCE – Fujisawa.

REFERENCES

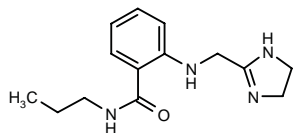
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2. Nakashima, M. et al. *Phase I study of FKK138 - Single dose study in healthy male volunteers.* Jpn Pharmacol Ther 2000, 28(12): 1047.
3. Oda, Y. et al. *Fibrin clot affinity and fibrin-dependent plasminogen activation of FKK138, a novel modified t-PA.* Jpn Pharmacol Ther 2000, 28(6): 499.
4. Oda, Y. et al. *Thrombolytic activity and reocclusion after thrombolysis of a novel modified human tissue-type plasminogen activator, FKK138, in a canine model of coronary artery thrombosis.* Jpn Pharmacol Ther 2000, 28(6): 519.
5. Oda, Y. et al. *Thrombolytic activity of a novel modified human tissue-type plasminogen activator, FKK138, in a canine model of copper coil-induced coronary artery thrombi.* Jpn Pharmacol Ther 2000, 28(6): 507.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

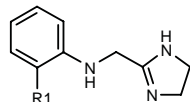
296777

2-(4,5-Dihydro-1*H*-imidazol-2-ylmethylamino)-*N*-propylbenzamide



C14 H20 N4 O; Mol wt: 260.3390

ACTION – α_{1A} -Adrenoceptor agonist with potential in the treatment of nasal congestion, priapism, depression, anxiety, dementia, senility, Alzheimer’s disease, obesity, bulimia, anorexia and particularly urinary incontinence. Other specifically claimed compounds from this series of imidazoline derivatives include the following:



Compound	R1	Formula
296778	CON(Me)Et	C ₁₄ H ₂₀ N ₄ O
296779	2-Me-4-thiazolyl	C ₁₄ H ₁₆ N ₄ S
296780	1-Me-2-pyrrolyl	C ₁₅ H ₁₈ N ₄
296781	1-(CF ₃ CH ₂)-1,2,4-triazol-5-yl	C ₁₄ H ₁₅ F ₃ N ₆
296782	1- <i>i</i> -Pr-1,2,4-triazol-5-yl	C ₁₅ H ₂₀ N ₆

SOURCE – GlaxoSmithKline.

REFERENCES

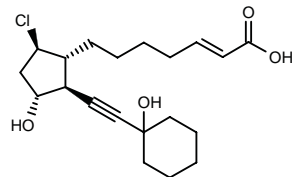
1. Bigham, E.C. et al. (Glaxo Group Ltd.) *Imidazoline derivs. as α_{1A} adrenoceptor ligands*. WO 0066563.

TREATMENT OF RENAL DISEASES

297225

7-[(1*R*,2*S*,3*R*,5*R*)-5-Chloro-3-hydroxy-2-[(1-hydroxycyclohexyl)ethynyl]cyclopentyl]-2(*E*)-heptenoic acid

9-Chloro-11-(1-hydroxycyclohexyl)-9-deoxy-2,3,13,14-tetrahydro-15,16,17,18,19,20-hexanorprostaglandin F_{1 β}



C20 H29 Cl O4; Mol wt: 368.8981

ACTION – A representative compound from a series of prostaglandin derivatives with prostaglandin D₂ (PGD₂)-like agonist activity, proven to increase cAMP production *in vitro* in bovine fetal trachea-derived cells. Potentially useful in the treatment of nephropathies, as well as cardiovascular disorders such as ischemic cardiopathy, hypertension and heart failure.

SOURCE – Taisho.

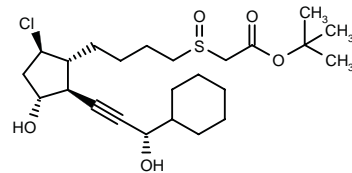
REFERENCES

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297360

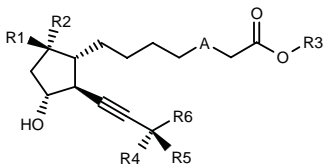
2-[4-[(1*R*,2*S*,3*R*,5*R*)-5-Chloro-2-[3(*S*)-cyclohexyl-3-hydroxy-1-propynyl]-3-hydroxycyclopentyl]butylsulfinyl]-acetic acid *tert*-butyl ester

9-Chloro-15-cyclohexyl-9-deoxy-13,14-didehydro-16,17,18,19,20-pentanor-3-thiaprostaglandin F_{1 β} *tert*-butyl ester *S*-oxide



C24 H39 Cl O5 S; Mol wt: 475.0861

ACTION – Agent for the treatment of nephropathies, as well as cardiovascular disorders such as ischemic cardiopathy, hypertension and heart failure, that exhibits prostaglandin D₂ (PGD₂)-like agonist activity. A representative compound from a series of prostaglandin derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
297361	Cl	H	H	H	OH	cyclohexyl	SO	C ₂₀ H ₃₁ ClO ₅ S
297362	H	Br	H	H	OH	cyclohexyl	SO ₂	C ₂₀ H ₃₁ BrO ₆ S
297363	H	Br	Me	OH	H	cyclohexyl	SO ₂	C ₂₁ H ₃₃ BrO ₆ S
297364	Cl	H	Me	OH	H	cyclopentyl	SO ₂	C ₂₀ H ₃₁ ClO ₆ S
297365	Br	H	H	OH	H	cyclopentyl	SO ₂	C ₁₉ H ₂₉ BrO ₆ S
297366	Br	H	Me	OH	H	cyclopentyl-CH ₂	SO ₂	C ₂₁ H ₃₃ BrO ₆ S
297368	Cl	H	H	OH	H	(R)-CH ₂ CH(Me)Bu	SO ₂	C ₂₁ H ₃₅ ClO ₆ S
297369	Cl	H	H	OH	H	(R)-CH(Me)CH ₂ -ethynyl-Et	SO ₂	C ₂₁ H ₃₁ ClO ₆ S

SOURCE – Taisho.

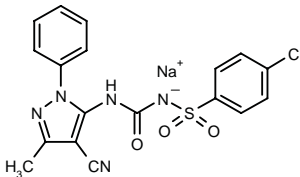
REFERENCES

1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin derivs.* JP 2000273082.

SM-19712*

255069

N-(4-Chlorophenylsulfonyl)-N'-(4-cyano-3-methyl-1-phenylpyrazol-5-yl)urea sodium salt



C18 H13 Cl N5 Na O3 S; Mol wt: 437.8417

ACTION – Potent, nonpeptide inhibitor of endothelin-converting enzyme (ECE; IC₅₀ = 42 nM) with high selectivity over other metalloproteases such as angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP), as well as against various receptors or enzymes. *In vivo*, compound suppressed the pressor response to big ET-1 after either i.v. (ED₅₀ = 5.6 mg/kg) or p.o. administration (37.2% at 30 mg/kg). In a rabbit model of myocardial infarction, it significantly reduced infarct size and serum concentrations of ET-1, as well as serum activity of creatinine phosphokinase. Moreover in a model of ischemic acute renal failure in rats, compound was able to dose-dependently attenuate the impairment of renal function, as well as the severe renal damage (tubular necrosis, proteinaceous casts in tubuli and medullary congestion) induced by occlusion of the left renal artery. Pharmacokinetic studies in rats showed a rapid decrease in plasma levels after i.v. administration (t_{1/2} = 16 min), low oral bioavailability (8%) and high serum protein binding (99%). Potentially useful for the treatment of cardiovascular diseases and ischemic acute renal failure.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Matsushita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Sulfonylureidopyrazole derivs.* EP 0885890, JP 1998007658, WO 9730978.

2. Matsumura, Y. et al. *Protective effect of SM-19712, a novel and potent endothelin converting enzyme inhibitor, on ischemic acute renal failure in rats.* Jpn J Pharmacol 2000, 84(1): 16.

3. Umekawa, K. et al. *Pharmacological characterization of a novel sulfonylureid-pyrazole derivative, SM-19712, a potent nonpeptidic inhibitor of endothelin converting enzyme.* Jpn J Pharmacol 2000, 84(1): 7.

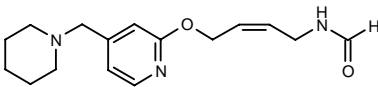
*Identified compound **255069** Drug Data Rep 1998, 020(01): 0041.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

296900

N-[4-[4-(1-Piperidinylmethyl)pyridin-2-yloxy]-2(Z)-butenyl]formamide



C16 H23 N3 O2; Mol wt: 289.3767

ACTION – Histamine H₂ receptor antagonist and acid secretion inhibitor proven to inhibit histamine-induced heart rate increase in isolated guinea pig heart by 73.8% at 1 μM. Potentially useful for the treatment of gastritis, gastric ulcer, duodenal ulcer, upper gastrointestinal bleeding and Zollinger-Ellison syndrome.

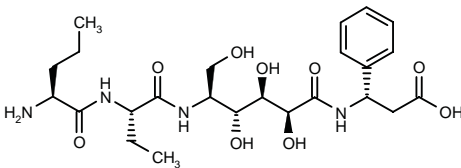
SOURCE – Taisho.

REFERENCES

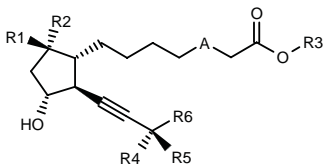
1. Suzuki, M. and Arai, M. (Taisho Pharmaceutical Co., Ltd.) *Piperidinomethylpyridine derivs.* JP 2000256353.

296901

3(S)-[2(S),3(R),4(R),6-Tetrahydroxy-5(S)-[2(S)-(L-norvalylamino)butyramido]hexanamido]-3-phenylpropionic acid



C24 H38 N4 O9; Mol wt: 526.5832



Compound	R1	R2	R3	R4	R5	R6	A	Formula
297361	Cl	H	H	H	OH	cyclohexyl	SO	C ₂₀ H ₃₁ ClO ₅ S
297362	H	Br	H	H	OH	cyclohexyl	SO ₂	C ₂₀ H ₃₁ BrO ₆ S
297363	H	Br	Me	OH	H	cyclohexyl	SO ₂	C ₂₁ H ₃₃ BrO ₆ S
297364	Cl	H	Me	OH	H	cyclopentyl	SO ₂	C ₂₀ H ₃₁ ClO ₆ S
297365	Br	H	H	OH	H	cyclopentyl	SO ₂	C ₁₉ H ₂₉ BrO ₆ S
297366	Br	H	Me	OH	H	cyclopentyl-CH ₂	SO ₂	C ₂₁ H ₃₃ BrO ₆ S
297368	Cl	H	H	OH	H	(R)-CH ₂ CH(Me)Bu	SO ₂	C ₂₁ H ₃₅ ClO ₆ S
297369	Cl	H	H	OH	H	(R)-CH(Me)CH ₂ -ethynyl-Et	SO ₂	C ₂₁ H ₃₁ ClO ₆ S

SOURCE – Taisho.

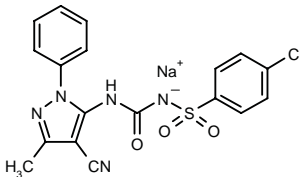
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SM-19712*

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SOURCE – Sumitomo Pharmaceuticals.

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- 1. Matsushita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Sulfonylureidopyrazole derivs.* EP 0885890, JP 1998007658, WO 9730978.
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- 3. Umekawa, K. et al. *Pharmacological characterization of a novel sulfonylureid-pyrazole derivative, SM-19712, a potent nonpeptidic inhibitor of endothelin converting enzyme.* Jpn J Pharmacol 2000, 84(1): 7.

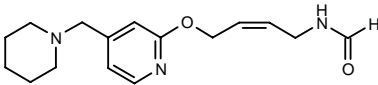
*Identified compound **255069** Drug Data Rep 1998, 020(01): 0041.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

296900

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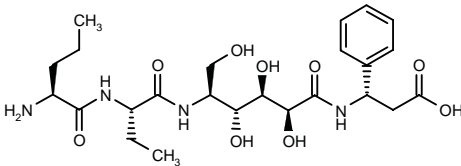
SOURCE – Taisho.

REFERENCES

1. Suzuki, M. and Arai, M. (Taisho Pharmaceutical Co., Ltd.) *Piperidinomethylpyridine derivs.* JP 2000256353.

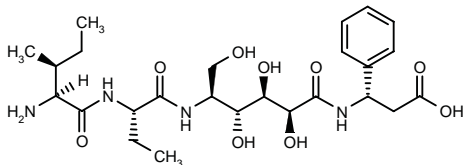
296901

3(S)-[2(S),3(R),4(R),6-Tetrahydroxy-5(S)-[2(S)-(L-norvalylamino)butyramido]hexanamido]-3-phenylpropionic acid



C24 H38 N4 O9; Mol wt: 526.5832

ACTION – Agent with potent activity against *Helicobacter pylori* (MIC = 0.006 µg/ml or less against *H. pylori* NCTC11637). *In vivo*, it completely suppressed gastric bacterial counts in Mongolian gerbils infected with *H. pylori* TN2GF4 at a dose of 3 mg/kg b.i.d. p.o. x 7 days when given as a gastric mucosal adhesive formulation (ADMMS). Another exemplified compound from this series of polyols is:



296902: C25 H40 N4 O9

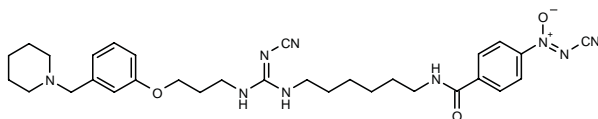
SOURCE – Takeda.

REFERENCES

1. Kamiyama, K. et al. (Takeda Chemical Industries, Ltd.) *Polyols, their preparation method, and use*. JP 2000256395.

299804

4-(Cyano-*NNO*-azoxy)-*N*-[6-[*N*²-cyano-*N*³-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]guanidino]hexyl]benzamide



C31 H41 N9 O3; Mol wt: 587.7249

ACTION – Agent that combines an antisecretory (H_2 antagonist) pharmacophore with the antibiotic calvatic acid in a single molecule. In isolated guinea pig atria, compound (30 µM) irreversibly antagonized the effect of histamine. Activity against *H. pylori* was demonstrated *in vitro* against 20 clinical strains: compound showing activity comparable to metronidazole (MIC₉₀ = 2 and 8 µg/ml, respectively) against metronidazole-sensitive and -resistant strains. *In vivo* studies to evaluate the antisecretory and anti-*H. pylori* activity of compound are in progress.

SOURCES – Università degli Studi di Milano, Milano (IT); Università degli Studi del Piemonte Orientale, Novara (IT); Università degli Studi “La Sapienza”, Roma (IT); Università degli Studi di Torino, Torino (IT).

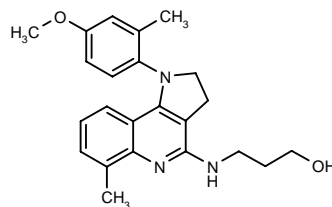
REFERENCES

1. Sorba, G. et al. *Anti-Helicobacter pylori agents endowed with H₂-antagonist properties*. Bioorg Med Chem Lett 2001, 11(3): 403.

DBM-819

299718

3-[1-(4-Methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-ylamino]-1-propanol



C23 H27 N3 O2; Mol wt: 377.4853

ACTION – Potent, reversible and noncompetitive gastric H^+/K^+ -ATPase inhibitor with an IC₅₀ value of 5 µM against rabbit enzyme compared to 22.4 µM for omeprazole. *In vivo*, compound inhibited basal acid secretion when given intraduodenally to pylorus-ligated rats (ED₅₀ = 3.5 mg/kg) and reduced both histamine- and pentagastrin-stimulated gastric secretion (ED₅₀ = 4.0 and 5.1 mg/kg, respectively) in lumen-perfused rats. Oral administration of compound protected against gastric lesions induced by ethanol, NaOH, indomethacin and aspirin with respective ED₅₀ values of 7.0, 20, 3.1 and 4.4 mg/kg. Moreover, compound reduced duodenal damage induced by cysteamine with an ED₅₀ value of 6.0 mg/kg. Potentially useful for the treatment of acid-related diseases.

SOURCES – Dongbu Hannong Chemical; Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

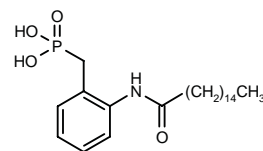
1. Cheon, H.G. et al. *Biochemical properties of a newly synthesized H⁺/K⁺ ATPase inhibitor, 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl) amino]-6-methyl-2,3-dihydropyrrolo[3, 2-*c*]quinoline*. Eur J Pharmacol 2001, 411(1-2): 181.

2. Cheon, H.G. et al. *Pharmacological properties of a newly synthesized H⁺/K⁺ ATPase inhibitor, 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl) amino]-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline*. Eur J Pharmacol 2001, 411(1-2): 187.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

297663

2-(Hexadecanoylamino)benzylphosphonic acid



C23 H40 N O4 P; Mol wt: 425.5460

ACTION – A representative compound from a series of phosphonic acid derivatives with sphingomyelinase-inhibitory activity (IC₅₀ = 0.54 µM for inhibition of human placenta-derived sphingomyelinase). Potentially useful for the treatment of fulminant hepatitis, type 1 and 2 diabetes, multiple sclerosis, chronic rheumatoid arthritis, transplant rejection, shock, cerebral or cardiac ischemia, among other disorders.

SOURCE – Ono.

REFERENCES

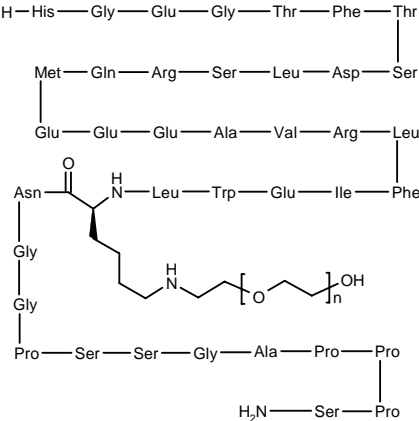
1. Matsui, T. et al. (Ono Pharmaceutical Co., Ltd.) *Phosphonic acid derivs.* JP 2000302793.

ENDOCRINE DRUGS

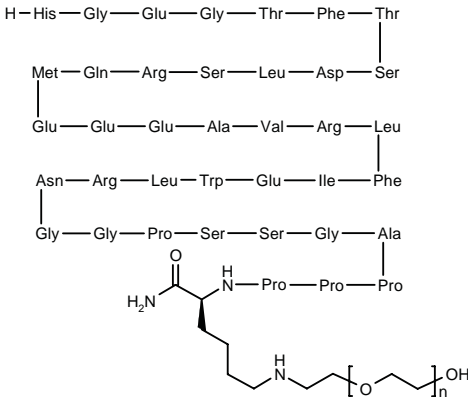
ANTIDIABETIC DRUGS

296869

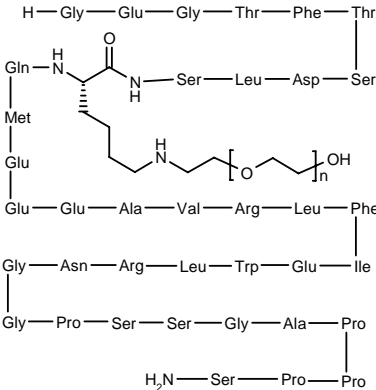
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Arg-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-(N^ε-PEG)Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂



ACTION – PEG-modified exendin, potentially useful for the treatment of diabetes, for regulating gastrointestinal motility and for reducing food intake. The compound demonstrated GLP-1 cyclase-activating activity (EC₅₀ = 0.8 nM) and reduced food intake in normal mice (ED₅₀ = 0.12 µg/kg i.p.). Other exemplified compounds include the following:



296870



296871

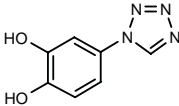
SOURCE – Amylin.

REFERENCES

1. Young, A. and Prickett, K. (Amylin Pharmaceuticals, Inc.) *Modified exendins and exendin agonists.* WO 0066629.

296904

4-(1*H*-Tetrazol-1-yl)benzene-1,2-diol



C7 H6 N4 O2; Mol wt: 178.1504

ACTION – Antidiabetic agent, an inhibitor of tyrosine phosphatases. Compound exhibited IC₅₀ values of 32 and 47 µg/ml, respectively, against tyrosine phosphatase derived from CD45 membrane of Jurkat cells and recombinant protein-tyrosine-phosphatase PTP1B.

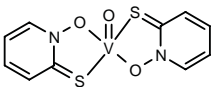
SOURCES – Kaneka; Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

1. Takeuchi, T. and Umezawa, K. (Microbial Chemistry Research Foundation;Kaneka Corp.) *Tyrosine phosphatase inhibitors.* JP 2000256330.

297456

Bis(2-thioxo-1,2-dihydropyridin-1-olato-*O,S*)oxovanadium



C10 H8 N2 O3 S2 V; Mol wt: 319.2582

ACTION – A representative compound from a series of oxovanadium complexes of 2-mercaptopyridine-*N*-oxides that reduce free fatty acid and blood sugar levels and are thus useful for the treatment of diabetes and hypertension. This compound significantly decreased blood sugar levels in streptozotocin-diabetic rats when administered at an oral dose of 10 mg/kg.

SOURCE – Ono.

REFERENCES

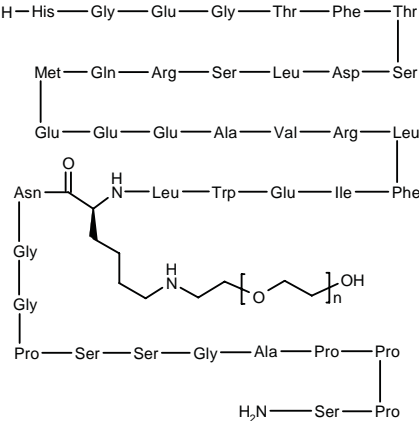
1. Matsui, T. et al. (Ono Pharmaceutical Co., Ltd.) *Phosphonic acid derivs.* JP 2000302793.

ENDOCRINE DRUGS

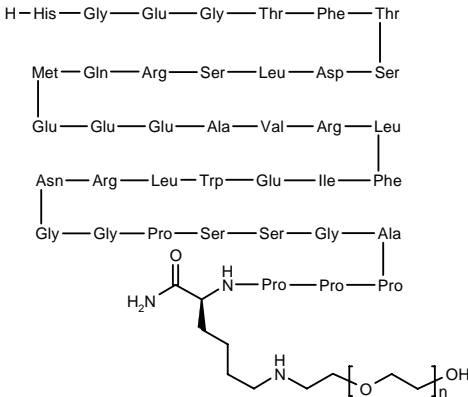
ANTIDIABETIC DRUGS

296869

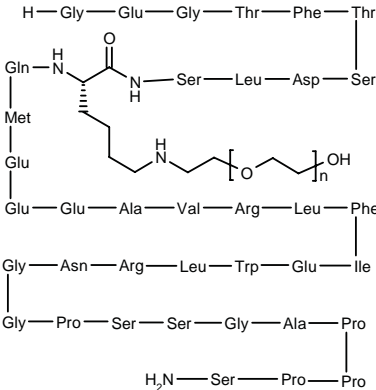
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Arg-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-(N^ε-PEG)Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂



ACTION – PEG-modified exendin, potentially useful for the treatment of diabetes, for regulating gastrointestinal motility and for reducing food intake. The compound demonstrated GLP-1 cyclase-activating activity (EC₅₀ = 0.8 nM) and reduced food intake in normal mice (ED₅₀ = 0.12 µg/kg i.p.). Other exemplified compounds include the following:



296870



296871

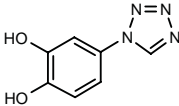
SOURCE – Amylin.

REFERENCES

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4-(1*H*-Tetrazol-1-yl)benzene-1,2-diol



C7 H6 N4 O2; Mol wt: 178.1504

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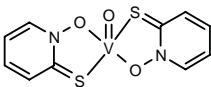
SOURCES – Kaneka; Microbial Chemistry Research Foundation, Tokyo (JP).

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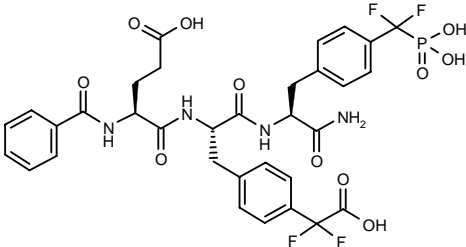
SOURCE – Japan Science and Technology.

REFERENCES

1. Sakurai, H. and Kojima, Y. (Japan Science and Technology Corp.) *Oxovanadium (IV) complex containing 2-mercapto-pyridine-N-oxide derivs.* JP 2000281650.

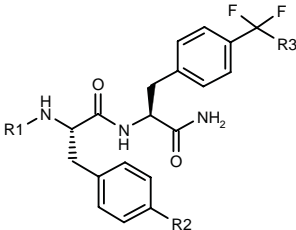
297517

N-Benzoyl-L-glutamyl-4-(1-carboxy-1,1-difluoromethyl)-L-phenylalanyl-4-(1,1-difluoro-1-phosphonomethyl)-L-phenylalaninamide



C33 H33 F4 N4 O11 P; Mol wt: 768.6067

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor, potentially useful for the treatment of type 1 or type 2 diabetes, glucose intolerance, insulin resistance, obesity, cancer and neurodegenerative diseases. Other specifically claimed phosphonic and carboxylic acid derivatives are:



Compound	R1	R2	R3	Formula
297519	PhCH2-L-Glu-	CF2PO(OH)2	CO2H	C ₃₃ H ₃₃ F ₄ N ₄ O ₁₁ P
297520	COPh	OH	PO3H2	C ₂₆ H ₂₆ F ₂ N ₃ O ₇ P
297522	COPh	CF2CO2H	PO3H2	C ₂₈ H ₂₆ F ₄ N ₃ O ₈ P

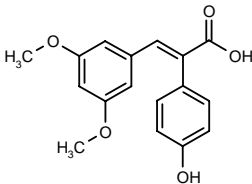
SOURCE – Merck Frosst.

REFERENCES

1. Leblanc, Y. et al. (Merck Frosst Canada Inc.) *Phosphonic and carboxylic acid derivs. as inhibitors of protein tyrosine phosphatase-1B (PTP-1B).* WO 0069889.

297533

3-(3,5-Dimethoxyphenyl)-2-(4-hydroxyphenyl)-2-propenoic acid



C17 H16 O5; Mol wt: 300.3084

ACTION – Orally active antidiabetic agent proven to decrease blood glucose levels in rats with streptozotocin-induced diabetes at 20 mg/kg p.o. When tested in hyperinsulinemic and insulin-resistant Zucker (*fa/fa*) rats, compound was shown to improve glucose tolerance, as well as to decrease plasma triglyceride and insulin levels, at a dose of 20 mg/kg p.o. No mortality was observed following administration of 333 mg/kg p.o. to mice.

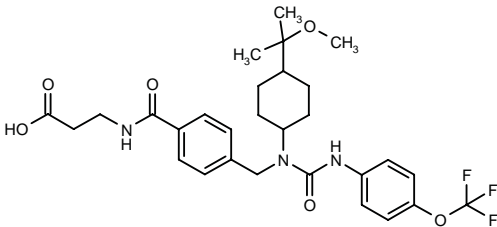
SOURCE – Calyx Therapeutics.

REFERENCES

1. Nag, B. et al. (Calyx Therapeutics Inc.) *Novel diphenylethylene cpds.* WO 0069430.

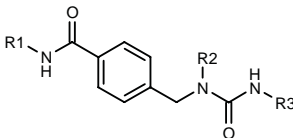
297565

N-[4-[1-[4-(1-Methoxy-1-methylethyl)cyclohexyl]-3-[4-(trifluoromethoxy)phenyl]ureidomethyl]benzoyl]-β-alanine



C29 H36 F3 N3 O6; Mol wt: 579.6124

ACTION – Glucagon antagonist/inverse agonist that is especially indicated for metabolic disorders such as hyperglycemia, impaired glucose tolerance, type 1 diabetes, type 2 diabetes and obesity. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
297566	CH2CH2CO2H	trans-4-t-Bu-cyclohexyl	3,4-(Cl)2-Ph	C ₂₈ H ₃₆ Cl ₂ N ₃ O ₄
297567	CH2CH2CO2H	t-BuCH2	4-(CO2Bu)-Ph	C ₂₈ H ₃₇ N ₃ O ₆
297568	CH2CH2CO2H	4-Cl-PhCH2CH2	4-(PhCH2O)-Ph	C ₃₃ H ₃₂ ClN ₃ O ₅
297569	2H-tetrazol-5-yl	4-cyclohexyl-Ph	4-Br-Ph-CH(Me)	C ₃₀ H ₃₂ BrN ₇ O ₂
297570	2H-tetrazol-5-yl	4-cyclohexyl-Ph	2,6-(F)2-Ph-CH2	C ₂₉ H ₂₉ F ₂ N ₇ O ₂
297571	2H-tetrazol-5-yl	4-(1-cyclohexenyl)-Ph	4-Br-Ph-CH(Me)	C ₃₀ H ₃₀ BrN ₇ O ₂
297572	2H-tetrazol-5-yl	4-(1-cyclohexenyl)-Ph	2,6-(F)2-Ph-CH2	C ₂₉ H ₂₇ F ₂ N ₇ O ₂

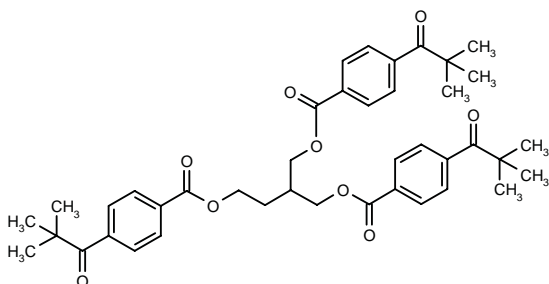
SOURCES – Agouron (Pfizer); Novo Nordisk.

REFERENCES

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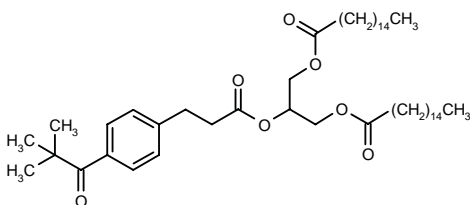
299590

4-(2,2-Dimethyl-1-oxopropyl)benzoic acid 2-[4-(2,2-dimethyl-1-oxopropyl)benzoyloxymethyl]-1,4-butanediyl diester



C41 H48 O9; Mol wt: 684.8212

ACTION – Hypoglycemic agent, a prodrug of a CoA-sequestering agent which is metabolically transformed to the active compound in the liver, without reaching the general circulation, and is therefore devoid of peripheral toxicity. The active compound inhibits fatty acid oxidation and liver glucose production. The ester prodrug reduced glucose levels in streptozotocin-diabetic rats ($ED_{50} = 39$ mg/kg/day p.o.) over 28 days, without releasing the active species into the circulation, as demonstrated by an undetectable AUC. Moreover, consistent with the AUC data, no testicular toxicity was detected in rats at doses 10-fold higher than the hypoglycemic doses. Selected as a development candidate for the treatment of the hyperglycemia associated with type 2 diabetes. Another active prodrug is:



299592: C49 H84 O7

SOURCE – Novartis.

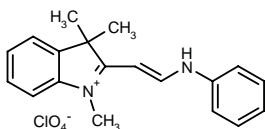
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1. Beberitz, G.R. et al. *Reduction in glucose levels in STZ diabetic rats by 4-(2,2-dimethyl-1-oxopropyl)benzoic acid: A prodrug approach for targeting the liver.* J Med Chem 2001, 44(4): 512.

YM-126414

299015

1,3,3-Trimethyl-2-(2-phenylvinyl)-3H-indolium perchlorate



C19 H21 N2 . Cl O4; Mol wt: 376.8379

ACTION – Potential antidiabetic agent proven to stimulate *in vitro* glucose uptake by skeletal muscle cells, apparently via activation of glucose transporter GLUT4 redistribution to the plasma membrane. In murine myoblast C2C12 cells, compound increased the rate of glucose consumption with an EC_{50} of 10 nM, and in fully differentiated C2C12 cells, but not undifferentiated muscle cells, it strongly increased GLUT4 redistribution with an EC_{50} of 21 nM.

SOURCE – Yamanouchi.

REFERENCES

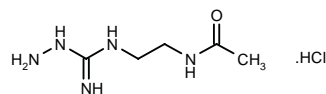
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TREATMENT OF DIABETIC COMPLICATIONS

ALT-946*

273917

N-[2-(N-Aminoguanidino)ethyl]acetamide hydrochloride



C5 H13 N5 O . HCl; Mol wt: 195.6526

ACTION – Agent for preventing or delaying the development of diabetic nephropathy, an inhibitor of advanced glycation end product (AGE) formation with an IC_{50} value of 3.4 mM for inhibition of AGE–protein crosslinking *in vitro*, compared to an IC_{50} value of 13.4 mM for aminoguanidine. *In vivo* in diabetic rats, compound given for 8 weeks at the dose of 0.03 mg/kg/day induced a normalization of the increased IgG crosslinking to red blood cells and a normalization of albuminuria and glomerular filtration; no significant effects were seen on body weight, glycemic control or blood pressure and the treated animals also showed reduced glomerular AGE staining compared to diabetic controls.

SOURCE – Alteon.

REFERENCES

1. Ulrich, P.C. and Waggle, D.R. (Alteon Inc.) *N-Acylaminoalkyl-hydrazinecarboximidamides.* US 5877217.
2. Forbes, J.M. et al. *Renoprotective effects of a novel inhibitor of advanced glycation.* Diabetologia 2001, 44(1): 108.
3. Goyan, J.E. *The A.G.E. pathway: Current approaches to therapeutic intervention.* IBC Post-Conf Workshop - Drug Discov Dev Diabet Complicat (Nov 1, Washington DC) 1996, 1996.

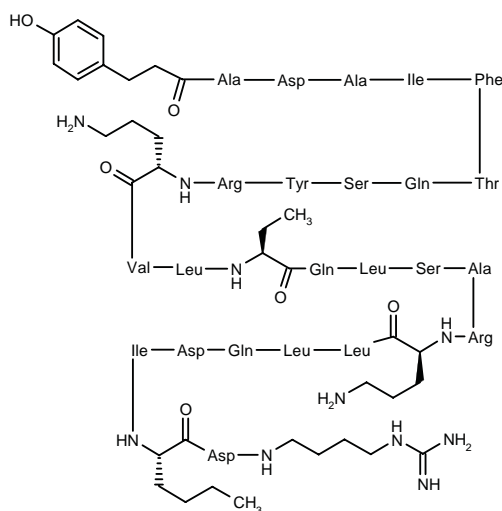
*Identified compound **273917** Drug Data Rep 1999, 021(05): 0429.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

Jl-38

299666

N-[3-(4-Hydroxyphenyl)propionyl]-L-alanyl-L-aspartyl-L-alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-glutaminy-L-seryl-L-tyrosyl-L-arginyl-L-ornithyl-L-valyl-L-leucyl-L-(2-aminobutyryl)-L-glutaminy-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-ornithyl-L-leucyl-L-leucyl-L-glutaminy-L-aspartyl-L-isoleucyl-L-norleucyl-L-aspartic acid *N*²-[4-(guanidino)-butyl]amide



C151 H248 N42 O42; Mol wt: 3323.8720

ACTION – Growth hormone-releasing hormone (GHRH) superagonist with high binding affinity for membrane receptors of rat anterior pituitary cells, with relative potency of 16.81 compared with the standard analogue hGHRH-(1-29)-NH₂. In rats, compound released GH after both s.c. and i.v. administration with respective relative potencies of 71.4 and 7.4 at 15 min compared to hGHRH-(1-29)-NH₂. It stimulated the rate of proliferation of normal human diploid dermal fibroblasts (NHF) *in vitro* and induced about a 0.5-3.5-fold increase in the levels of mRNA for *c-myc* oncogene. In addition, in monosodium glutamate (MSG)-lesioned young rats, compound given at a dose of 2 µg at 12-h intervals for 2 weeks markedly stimulated growth, GH synthesis and IGF-I secretion, although basal serum GH levels did not change. Compound did not modify pituitary GHRH receptor concentration or binding affinity, and in normal rats it did not increase normal growth but stimulated GH synthesis and GH secretory responsiveness. Potentially useful for the treatment of GH deficiencies due to hypothalamic dysfunction, as well as for conditions requiring stimulation of cell proliferation such as wound healing and tissue regeneration.

SOURCES – Tulane University School of Medicine, New Orleans, LA (US); Veterans Administration Medical Center, New Orleans, LA (US).

REFERENCES

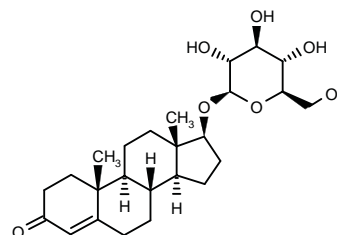
- Schally, A.V. and Izdebski, J. (Tulane Educational Fund) *Novel highly potent agonists of growth hormone releasing hormone*. EP 0809507, JP 1998512881, WO 9622782.
- Izdebski, J. et al. *Synthesis and biological evaluation of superactive agonists of growth hormone-releasing hormone*. Proc Natl Acad Sci USA 1995, 92: 4872.
- Kiaris, H. et al. *Direct action of growth hormone-releasing hormone agonist Jl-38 on normal human fibroblasts: Evidence from studies on cell proliferation and c-myc proto-oncogene expression*. Regul Pept 2001, 96(3): 119.
- Kovacs, M. et al. *Chronic administration of a new potent agonist of growth hormone-releasing hormone induces compensatory linear growth in growth hormone-deficient rats: Mechanism of action*. Neuroendocrinology 1996, 64(3): 169.
- Kovacs, M. et al. *Increase in mRNA concentrations of pituitary receptors for growth hormone-releasing hormone and growth hormone secretagogues after neonatal monosodium glutamate treatment*. J Neuroendocrinol 2000, 12(4): 335.

TREATMENT OF MALE SEXUAL DYSFUNCTION

TESTOSTERONE GLUCOSIDE

296646

17β-(β-D-Glucopyranosyloxy)androst-4-en-3-one



C25 H38 O7; Mol wt: 450.5682

ACTION – A representative compound from a series of androgen glycoside derivatives that act as androgen prodrugs and are reported to be less susceptible to hepatic degradation following oral administration than the corresponding unglycosylated androgen, being only substantially deglycosylated after the first passage through the liver, which results in higher circulatory androgen levels. When administered either p.o. or i.m. to rats, compound was shown to result in increased plasmatic testosterone levels as compared to oral administration of testosterone.

SOURCE – Strakan.

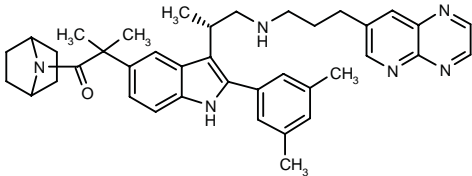
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TREATMENT OF GYNECOLOGICAL DISORDERS

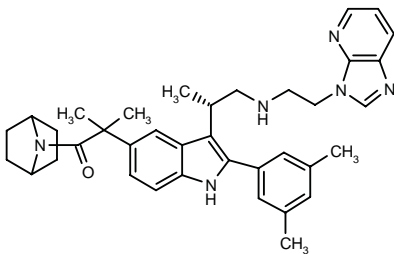
297354

N-[2(*S*)-[5-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl]-*N*-(3-pyrido[2,3-*b*]pyrazin-7-ylpropyl)amine



C39 H46 N6 O; Mol wt: 614.8334

ACTION – Gonadotropin-releasing hormone (GnRH or LHRH) antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women, including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Another exemplified compound from this series of indole derivatives is:



297355: C37 H44 N6 O

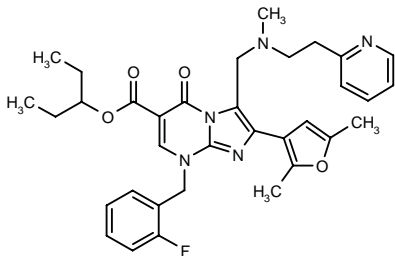
SOURCE – Merck & Co.

REFERENCES

1. Young, J.R. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. US 6159975.

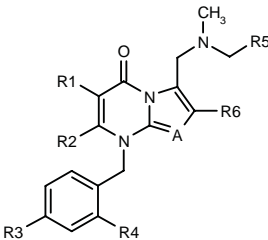
297798

2-(2,5-Dimethylfuran-3-yl)-8-(2-fluorobenzyl)-3-[*N*-methyl-*N*-[2-(2-pyridinyl)ethyl]aminomethyl]-5-oxo-5,8-dihydro-imidazo[1,2-*a*]pyrimidine-6-carboxylic acid 1-ethylpropyl ester



C34 H38 F N5 O4; Mol wt: 599.7032

ACTION – Gonadotropin-releasing hormone (GnRH) receptor antagonist, potentially useful for the treatment of sex hormone-related conditions in both men and women, including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, prostate, breast and ovarian cancer, pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as adjunctive treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed compounds from this series of imidazo- and pyrrolo[1,2-*a*]pyrimid-4-one derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
297799	3-MeO-Ph	Me	H	F	2-Pyr-CH2	2-thienyl	N	C ₃₄ H ₃₂ FN ₅ O ₂ S
297800	3-MeO-Ph	Me	H	F	2-Pyr-CH2	3-Pyr	N	C ₃₅ H ₃₃ FN ₆ O ₂
297802	CO2CH(Et)2	H	H	F	2-Pyr-CH2	2,5-(Me)2-3-furyl	CH	C ₃₅ H ₃₉ FN ₄ O ₄
297803	CO2Et	H	H	CN	Ph	4-MeO-Ph	C(CN)	C ₃₅ H ₃₁ N ₅ O ₄
297804	CO2Et	H	F	F	Ph	4-MeO-Ph	C(CN)	C ₃₄ H ₃₀ F ₂ N ₄ O ₄
297805	CO2Et	H	H	F	Ph	4-i-BuO-Ph	C(F)	C ₃₆ H ₃₇ F ₂ N ₃ O ₄

SOURCE – Neurocrine Biosciences.

REFERENCES

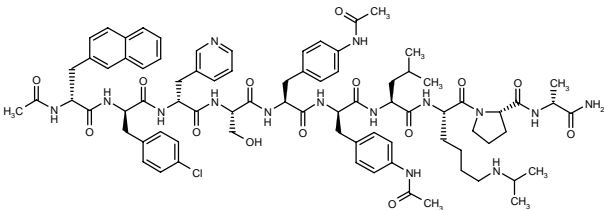
1. Zhu, Y.-F. et al. (Neurocrine Biosciences Inc.) *Imidazo- and pyrrolo[1,2-a]pyrimid-4-ones as gonadotropin-releasing hormone receptor antagonists*. WO 0069859.

AGENTS FOR FEMALE INFERTILITY

ACYLINE

299984

Acetyl-2-naphthyl-D-alanyl-4-chloro-D-phenylalanyl-3-pyridyl-D-alanyl-L-seryl-4-acetamido-L-phenylalanyl-4-acetamido-D-phenylalanyl-L-leucyl-*N*^ε-isopropyl-L-lysyl-L-prolyl-D-alaninamide



C80 H102 Cl N15 O14; Mol wt: 1533.2300

ACTION – Potent gonadotropin-releasing hormone (GnRH) antagonist ($pA_2 = 8.6$) reported to inhibit GnRH-mediated luteinizing hormone (LH) secretion from pituitary cells *in vitro* and to have high potency in the antiovarulatory assay in rats and long-lasting inhibitory activity on the release of LH in rats. A phase I study in healthy young men showed that compound significantly suppressed testosterone, LH and follicle-stimulating hormone (FSH) in a dose-dependent manner up to 25 µg/kg; the gonadotropin and testosterone levels remained fully suppressed for at least 48 h. In this trial, compound was 2-3-fold more potent than the GnRH antagonists Nal-Glu and Nal-Lys. No adverse events have been seen in animal or human studies. Potential for a depot effect at higher doses is undergoing examination.

SOURCES – Salk Institute for Biological Studies, La Jolla, CA (US); University of Washington, Seattle, WA (US).

REFERENCES

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2. Rivier, J.E.F. et al. (The Salk Institute for Biological Studies) *GnRH antagonists*. EP 0804471, JP 1998500397, US 5506207, WO 9525741.

3. Herbst, K.L. et al. *Acyline: A new more potent and long-acting GnRH antagonist*. J Invest Med 2001, 49(1): Abst 90.

CHORIOGONADOTROPIN ALFA

281118

Recombinant human chorionic gonadotropin (hCG) produced by genetically engineered Chinese hamster ovary (CHO) cells

CrhCG

ACTION – Recombinant luteinizing hormone (LH) analogue that binds to the LH/human chorionic gonadotropin (hCG) receptor in the ovary and stimulates late follicular maturation and resumption of oocyte meiosis, and initiates rupture of the preovulatory ovarian follicle, in the absence of an endogenous LH surge.

INDICATION – Treatment of female infertility, used to trigger ovulation in women with anovulation and to promote final maturation of eggs in the ovaries of women undergoing assisted reproductive technologies such as *in vitro* fertilization.

PRESENTATION – Single-dose vials of lyophilized powder for s.c. injection, 285 µg of recombinant human chorionic gonadotropin delivering 250 µg after reconstitution with the diluent (1 ml sterile water).

PROPRIETARY NAME – Ovidrel (US).

SOURCE – Serono.

REFERENCES

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2. Feldman, E. et al. *Clinical evaluation of a commercial preparation of human chorionic gonadotropin (hCG) in myelodysplastic syndrome (MDS)*. Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2608.

3. Filicori, M. et al. *Low-dose human chorionic gonadotropin therapy can improve sensitivity to exogenous follicle-stimulating hormone in patients with secondary amenorrhea*. Fertil Steril 1999, 72(6): 118.

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10. Quenby, S. and Farquharson, R.G. *Human chorionic gonadotropin supplementation in recurring pregnancy loss: A controlled trial*. Fertil Steril 1994, 62(4): 708.

11. Russo, I.H. et al. *Recombinant human chorionic gonadotropin (r-hGC) reduces the incidence and progression of mammary tumors in the rat*. 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 160.

12. Russo, J. et al. *Recombinant human chorionic gonadotropin (r-hGC) significantly reduces primary tumor cell proliferation in patients with breast cancer*. 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 161.

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14. Yamaguchi, K. et al. *Blocking 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase with MK-733 decreases the serum estradiol level but does not suppress its response to human chorionic gonadotropin (HCG) in patients with hypercholesterolemia*. 8th Int Cong Endocrinol (July 17-23, Kyoto) 1988, Abst 16-22-258.

15. *Ares-Serono files for approval of new infertility treatment*. DailyDrugNews.com (Daily Essentials) 1999, Oct 7.

16. *Ares-Serono: Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1999, May 18.

17. *First approval for recombinant drug for infertility*. DailyDrugNews.com (Daily Essentials) 2000, Oct 3.

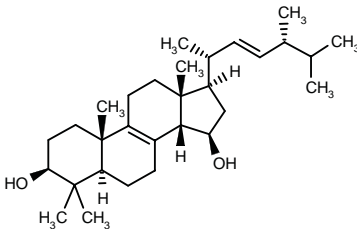
18. *Major advances in infertility treatment announced by Serono*. DailyDrugNews.com (Daily Essentials) 2001, Jan 5.

19. *Two innovative fertility products launched by Serono in U.S.* DailyDrugNews.com (Daily Essentials) 2001, Feb 5.

CONTRACEPTIVES

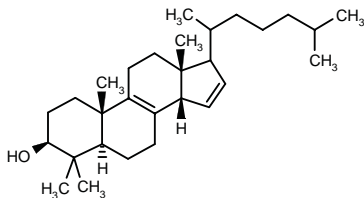
297067

(5α,14β)-4,4-Dimethylergosta-8,22(E)-diene-3β,15β-diol



C30 H50 O2; Mol wt: 442.7230

ACTION – Contraceptive agent that acts by inhibiting meiosis (100% inhibition in naked mouse oocytes). Another exemplified 14β-*H*-sterol is:



297068: C29 H48 O

SOURCE – Schering AG.

REFERENCES

1. Esperling, P. et al. (Schering AG) *14β-H-Sterols, pharmaceutical compsns. comprising them and use of these derivs. for the preparation of meiosis regulating medicaments*. WO 0068245.

GM-4

300241

Lipophilic submicron-particle-size gel microemulsion formulation whose components are: Captex 300, Cremophor EL, Phospholipon 90G, propylene glycol, PEG-200, Seaspan carrageenan, Viscarin carrageenan, sodium benzoate and water

ACTION – Microemulsion-based lipophilic vaginal spermicide shown to be much more effective than non-oxynol-9 gel in preventing pregnancy in ovulated rabbits when given intravaginally prior to artificial insemination (100% protection vs. 68.7% for nonoxynol-9). Rabbits treated with compound intravaginally for 10 days showed no epithelial ulceration, edema, leukocyte infiltration or vascular congestion, in contrast to animals treated with compound plus nonoxynol-9. In addition, in mice treated with intravaginal compound for 5 days/week for up to 13 weeks, no systemic toxicity or histopathological changes were detected. Potentially useful as a vaginal spermicide, and also for intravaginal delivery of antimicrobial agents to prevent the transmission of sexually transmitted diseases.

SOURCE – Parker Hughes Institute, Roseville, MN (US).

REFERENCES

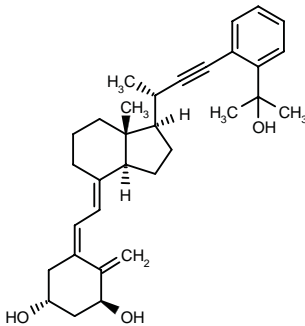
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DERMATOLOGIC DRUGS

ANTIPSORIATICS

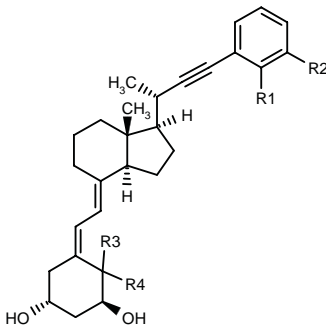
297113

(1*S*,3*R*,5*Z*,7*E*,20*R*)-23-[2-(1-Hydroxy-1-methylethyl)phenyl]-24-nor-9,10-secochola-5,7,10(19)-trien-22-yne-1,3-diol



C32 H42 O3; Mol wt: 474.6808

ACTION – Agent for the treatment and prevention of vitamin D disorders, particularly hyperproliferative skin disorders such as psoriasis, basal cell carcinoma, keratinization and keratosis, which exhibits vitamin D activity and low toxicity. Compound was shown to induce epidermal thickening with an ED₅₀ value of 10,000 µg/kg p.o. compared to 500 µg/kg p.o. for calcitriol, while the highest tolerated oral dose without inducing weight loss was 2000 µg/kg compared to 1 µg/kg for calcitriol, thus exhibiting a 100-fold improvement in the therapeutic margin compared to calcitriol. Other compounds from this series of arylsecocholadiene derivatives are:

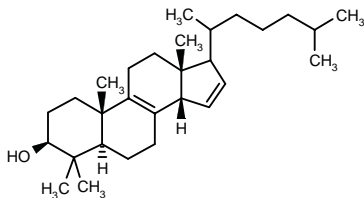


Compound	R1	R2	R3	R4	Formula
297114	CH(Me)2OH	H	H	H	C ₃₁ H ₄₂ O ₃
297115	H	CH(Me)2OH	CH2		C ₃₁ H ₄₂ O ₃

SOURCE – Roche.

REFERENCES

1. Barbier, P. et al. (Hoffmann-La Roche, Inc.) *Arylsecocholadiene derivs*. US 6153605.



297068: C29 H48 O

SOURCE – Schering AG.

REFERENCES

1. Esperling, P. et al. (Schering AG) *14β-H-Sterols, pharmaceutical compsns. comprising them and use of these derivs. for the preparation of meiosis regulating medicaments*. WO 0068245.

GM-4

300241

Lipophilic submicron-particle-size gel microemulsion formulation whose components are: Captex 300, Cremophor EL, Phospholipon 90G, propylene glycol, PEG-200, Seaspan carrageenan, Viscarin carrageenan, sodium benzoate and water

ACTION – Microemulsion-based lipophilic vaginal spermicide shown to be much more effective than non-oxynol-9 gel in preventing pregnancy in ovulated rabbits when given intravaginally prior to artificial insemination (100% protection vs. 68.7% for nonoxynol-9). Rabbits treated with compound intravaginally for 10 days showed no epithelial ulceration, edema, leukocyte infiltration or vascular congestion, in contrast to animals treated with compound plus nonoxynol-9. In addition, in mice treated with intravaginal compound for 5 days/week for up to 13 weeks, no systemic toxicity or histopathological changes were detected. Potentially useful as a vaginal spermicide, and also for intravaginal delivery of antimicrobial agents to prevent the transmission of sexually transmitted diseases.

SOURCE – Parker Hughes Institute, Roseville, MN (US).

REFERENCES

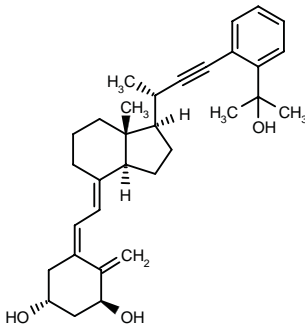
1. D'Cruz, O.J. et al. *Contraceptive efficacy and safety studies of a novel microemulsion-based lipophilic vaginal spermicide*. Fertil Steril 2001, 75(1): 115.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

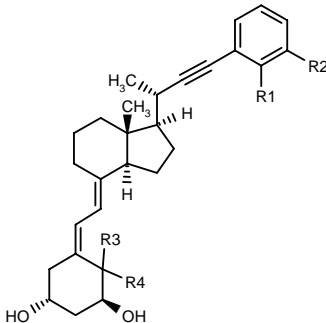
297113

(1*S*,3*R*,5*Z*,7*E*,20*R*)-23-[2-(1-Hydroxy-1-methylethyl)phenyl]-24-nor-9,10-secochola-5,7,10(19)-trien-22-yne-1,3-diol



C32 H42 O3; Mol wt: 474.6808

ACTION – Agent for the treatment and prevention of vitamin D disorders, particularly hyperproliferative skin disorders such as psoriasis, basal cell carcinoma, keratinization and keratosis, which exhibits vitamin D activity and low toxicity. Compound was shown to induce epidermal thickening with an ED₅₀ value of 10,000 µg/kg p.o. compared to 500 µg/kg p.o. for calcitriol, while the highest tolerated oral dose without inducing weight loss was 2000 µg/kg compared to 1 µg/kg for calcitriol, thus exhibiting a 100-fold improvement in the therapeutic margin compared to calcitriol. Other compounds from this series of arylsecocholadiene derivatives are:



Compound	R1	R2	R3	R4	Formula
297114	CH(Me)2OH	H	H	H	C ₃₁ H ₄₂ O ₃
297115	H	CH(Me)2OH	CH2		C ₃₁ H ₄₂ O ₃

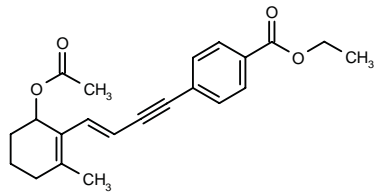
SOURCE – Roche.

REFERENCES

1. Barbier, P. et al. (Hoffmann-La Roche, Inc.) *Arylsecocholadiene derivs*. US 6153605.

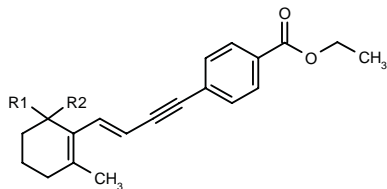
297128

(-)-4-[4-(6-Acetoxy-2-methyl-1-cyclohexen-1-yl)-3(*E*)-buten-1-ynyl]benzoic acid ethyl ester



C22 H24 O4; Mol wt: 352.4276

ACTION – A representative compound from a series of oxygen, sulfur and nitrogen substituted cyclohexene and cyclohexane derivatives having retinoid-like, retinoid-antagonist and/or retinoid inverse agonist-like biological activity. *In vitro*, compound was shown to inhibit TPA-induced ornithine decarboxylase (ODC) activity with an IC₆₀ value of 0.52 nM. Potentially useful for the treatment of skin-related diseases including keratoses, acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darier's disease and lichen planus, for the prevention and reversal of glucocorticoid damage, as a topical antimicrobial agent, as a skin antipigmentation agent and for the treatment and reversal of the effects of age and photodamage to the skin. Other exemplified compounds include the following:



Compound	R1	R2	Formula
297129	OAc	H	C ₂₂ H ₂₄ O ₄
297131	t-BuCOO	H	C ₂₅ H ₃₀ O ₄
297132	OCOPh	H	C ₂₇ H ₂₆ O ₄
297133	-N(OMe)-		C ₂₁ H ₂₃ NO ₃
297134	-CH(CO ₂ Et)-		C ₂₄ H ₂₆ O ₄

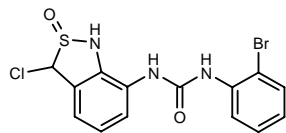
SOURCE – Allergan.

REFERENCES

1. Beard, R.L. et al. (Allergan, Inc.) *Oxygen, sulfur and nitrogen substd. cyclohexene and cyclohexane derivs. having retinoid-like biological activity*. WO 0068191.

297535

N-(2-Bromophenyl)-*N'*-(3-chloro-2-oxido-1,3-dihydro-2,1-benzisothiazol-7-yl)urea



C14 H11 Br Cl N3 O2 S; Mol wt: 400.6829

ACTION – IL-8 antagonist with the ability to bind to IL-8 α (CXCR1) or IL-8 β (CXCR2) receptors. This compound is useful for the treatment of IL-8-mediated diseases including psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft-vs.-host disease, allograft rejection, atherosclerosis, gingivitis and osteoporosis.

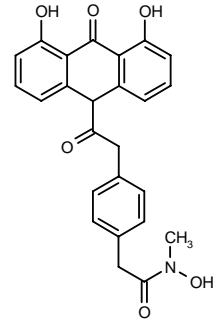
SOURCE – GlaxoSmithKline.

REFERENCES

1. Palovich, M.R. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0069435.

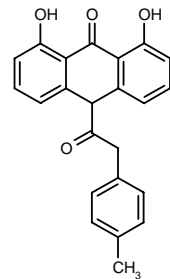
300093

2-[4-[2-(4,5-Dihydroxy-10-oxo-9,10-dihydroanthracen-9-yl)-2-oxoethyl]phenyl]-*N*-methylacetohydroxamic acid



C25 H21 N O6; Mol wt: 431.4419

ACTION – Potential antipsoriatic agent, a structural analogue of anthralin that retains the potent anti-proliferative activity of the parent compound against HaCaT keratinocytes (IC₅₀ = 0.7 μ M) combined with reduced hydroxyl radical formation and membrane damage. In addition, compound showed inhibitory activity against LTB₄ biosynthesis (IC₅₀ = 0.05 μ M) and, like anthralin, was able to induce terminal differentiation in HaCaT keratinocytes, measured as crosslinking of protein into cornified envelope-like structures. Within this series of 10-arylacetyl-anthracenones, the following is also described:



300094: C23 H18 O4

SOURCE – Teva.

REFERENCES

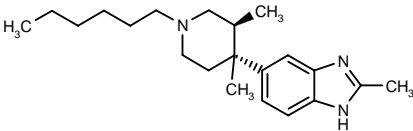
1. Muller, K. et al. (Teva Pharmaceutical Industries Ltd.) *10-Substd. 18-dihydroxy-9(10H)anthracenone pharmaceuticals*. US 5952390.

2. Müller, K. et al. *Antipsoriatic anthrones with modulated redox properties. 5. Potent inhibition of human keratinocyte growth. Induction of keratinocyte differentiation, and reduced membrane damage by novel 10-arylacetyl-1,8-dihydroxy-9(10H)-anthracenones*. J Med Chem 2001, 44(5): 814.

MISCELLANEOUS DERMATOLOGIC DRUGS

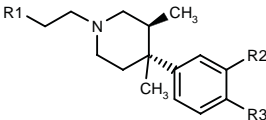
297268

(±)-trans-5-(1-Hexyl-3,4-dimethylpiperidin-4-yl)-2-methyl-1H-benzimidazole



C21 H33 N3; Mol wt: 327.5127

ACTION – Opioid receptor ligand with potential in the treatment of diseases modulated by opioid receptors such as irritable bowel syndrome, constipation, nausea, vomiting, and particularly pruritus. Other compounds from this series of 4-arylpiperidine derivatives include the following:



Compound	R1	R2,R3	Formula
297269	Bu	-N=C(OMe)NH-	C ₂₁ H ₃₃ N ₃ O
297270	Bu	-N=C(Et)NH-	C ₂₂ H ₃₅ N ₃
297271	3-Me-Ph	-N=C(CF ₃)NH-	C ₂₄ H ₂₈ F ₃ N ₃
297274	i-BuCH ₂	-N=CHNH-	C ₂₁ H ₃₃ N ₃
297276	Bu	-OC(Me)=N-	C ₂₁ H ₃₂ N ₂ O

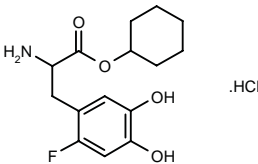
SOURCE – Pfizer.

REFERENCES

1. Armer, R.E. et al. (Pfizer Inc.;Pfizer Ltd.) *New 4-arylpiperidine derivs. for the treatment of pruritus*. EP 1055668.

297605

2-Fluoro-5-hydroxy-DL-tyrosine cyclohexyl ester hydrochloride



C15 H20 F N O4 . HCl; Mol wt: 333.7849

ACTION – Agent for the treatment of atopic dermatitis proven to inhibit compound 48/80-induced scratching in mice with an ED₅₀ of 129 mg/kg i.p.

SOURCE – Kyowa Hakko.

REFERENCES

1. Oshima, E. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Phenylalanine ester derivs. JP 2000297070*.

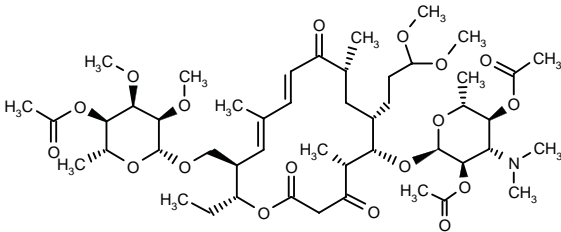
ANTIINFECTIVE THERAPY

ANTIBIOTICS

296816

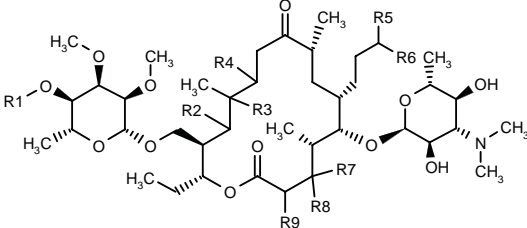
(4*R*,5*S*,6*S*,8*R*,10*E*,12*E*,14*R*,15*R*)-14-(4-*O*-Acetyl-6-deoxy-2,3-di-*O*-methyl-β-D-allopyranosyloxymethyl)-5-[2,4-di-*O*-acetyl-3,6-dideoxy-3-(dimethylamino)-α-D-glucopyranosyloxy]-6-(3,3-dimethoxypropyl)-4,8,12-trimethyl-3,9-dioxo-11,13-heptadecadieno-15-lactone

3-Deoxy-3-oxo-2',4',4''-triacetylidesmycosin 20-dimethyl-acetal



C48 H77 N O18; Mol wt: 956.1253

ACTION – Antibacterial tylosin derivative that may also be useful as an intermediate for the preparation of new compounds. Other exemplified 3-deoxy-3-oxodesmycosin derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	R9	Formula
296819	Ac	OH	bond		OMe	OMe	-O-	H		C ₄₄ H ₇₅ NO ₁₇
296820	H	H	H	H		-O-	H	bond		C ₄₀ H ₆₉ NO ₁₃

SOURCE – Pliva.

REFERENCES

1. Narandja, A. et al. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *3-Deoxy-desmycosin derivs. and process for their preparation*. WO 0066602.

SOURCE – Teva.

REFERENCES

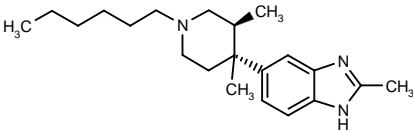
1. Muller, K. et al. (Teva Pharmaceutical Industries Ltd.) *10-Substd. 18-dihydroxy-9(10H)anthracenone pharmaceuticals*. US 5952390.

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MISCELLANEOUS DERMATOLOGIC DRUGS

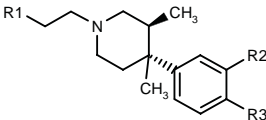
297268

(±)-*trans*-5-(1-Hexyl-3,4-dimethylpiperidin-4-yl)-2-methyl-1*H*-benzimidazole



C21 H33 N3; Mol wt: 327.5127

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297269	Bu	-N=C(OMe)NH-	C ₂₁ H ₃₃ N ₃ O
297270	Bu	-N=C(Et)NH-	C ₂₂ H ₃₅ N ₃
297271	3-Me-Ph	-N=C(CF ₃)NH-	C ₂₄ H ₂₈ F ₃ N ₃
297274	i-BuCH ₂	-N=CHNH-	C ₂₁ H ₃₃ N ₃
297276	Bu	-OC(Me)=N-	C ₂₁ H ₃₂ N ₂ O

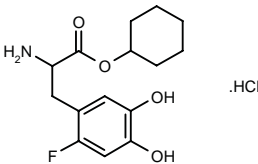
SOURCE – Pfizer.

REFERENCES

1. Armer, R.E. et al. (Pfizer Inc.;Pfizer Ltd.) *New 4-arylpiperidine derivs. for the treatment of pruritus*. EP 1055668.

297605

2-Fluoro-5-hydroxy-DL-tyrosine cyclohexyl ester hydrochloride



C15 H20 F N O4 . HCl; Mol wt: 333.7849

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SOURCE – Kyowa Hakko.

REFERENCES

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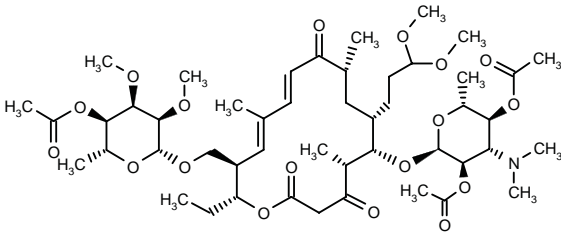
ANTIINFECTIVE THERAPY

ANTIBIOTICS

296816

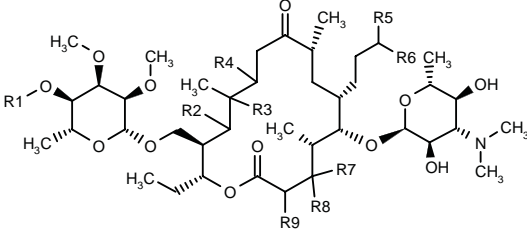
(4*R*,5*S*,6*S*,8*R*,10*E*,12*E*,14*R*,15*R*)-14-(4-*O*-Acetyl-6-deoxy-2,3-di-*O*-methyl-β-D-allopyranosyloxymethyl)-5-[2,4-di-*O*-acetyl-3,6-dideoxy-3-(dimethylamino)-α-D-glucopyranosyloxy]-6-(3,3-dimethoxypropyl)-4,8,12-trimethyl-3,9-dioxo-11,13-heptadecadieno-15-lactone

3-Deoxy-3-oxo-2',4',4''-triacetylidesmycosin 20-dimethyl-acetal



C48 H77 N O18; Mol wt: 956.1253

ACTION – Antibacterial tylosin derivative that may also be useful as an intermediate for the preparation of new compounds. Other exemplified 3-deoxy-3-oxodesmycosin derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	R9	Formula
296819	Ac	OH	bond		OMe	OMe	-O-	H		C ₄₄ H ₇₅ NO ₁₇
296820	H	H	H	H		-O-	H	bond		C ₄₀ H ₆₉ NO ₁₃

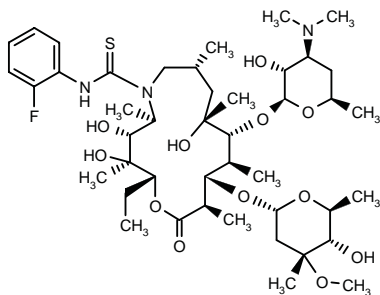
SOURCE – Pliva.

REFERENCES

1. Narandja, A. et al. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *3-Deoxy-desmycosin derivs. and process for their preparation*. WO 0066602.

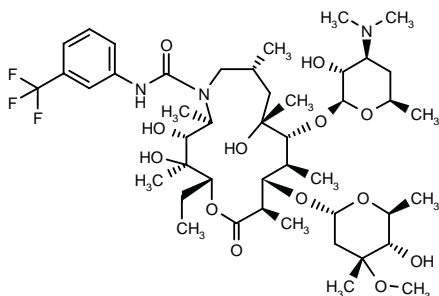
296821

9-Deoxo-9a-[N-(2-fluorophenyl)thiocarbamoyl]-9a-aza-homoerythromycin A



C44 H74 F N3 O12 S; Mol wt: 888.1416

ACTION – Antibacterial macrolide with a broad spectrum of activity including sensitive and resistant Gram-positive and Gram-negative microorganisms. Another exemplified compound from this series of halo derivatives of 9-deoxo-9a-aza-9a-homoerythromycin is:



296822: C45 H74 F3 N3 O13

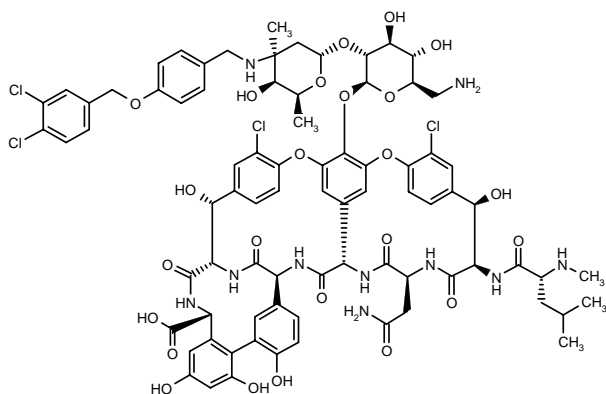
SOURCE – Pliva.

REFERENCES

1. Marusic-Istuk, Z. et al. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *Halo derivs. of 9-deoxo-9a-aza-9a-homerythromycin A*. WO 0066603.

297639

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-44-[2-*O*-[3-[4-(3,4-Dichlorobenzoyloxy)benzylamino]-3-*C*-methyl-2,3,6-trideoxy- α -L-galactopyranosyl]- β -D-glucopyranosyloxy]-3-(carbamoylmethyl)-10-chloro-7,22,28,30,32-penta-hydroxy-6-(*N*-methyl-D-leucylamino)-2,5,24,38,39-penta-oxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradeca-hydro-1*H*,22*H*-8,11:18,21-dietheno-23,26-(imino-methano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclo-tetracosine-26-carboxylic acid



C80 H86 Cl4 N10 O24; Mol wt: 1713.4170

ACTION – Antibacterial agent, a representative compound from a series of vancomycin analogues that exhibit enhanced biological activity and improved physicochemical and pharmacological properties; in particular, these compounds are reported to be active against many Gram-positive microorganisms including vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). *In vitro*, compound exhibited MIC values of 0.008-0.03, < 0.03-0.25, 0.008-0.03, 0.12-0.25, 0.12-0.5, 0.03-0.06 and 8-16 μ g/ml, respectively, against *Enterococcus faecium* RLA1, *Enterococcus faecalis* MB2864, MSSA MB2985, MRSA CL3033, VISA/MRSA CL5705 and MRCNS CL3069, compared to MIC values of 2, 2, 1, 0.5-1, 2-4 and 2 μ g/ml for vancomycin. In addition, it was found to be more effective than vancomycin against *S. aureus* MB2895-induced septicemia in mice, ED₅₀ values being 0.390 and 1.167 mg/kg s.c., respectively.

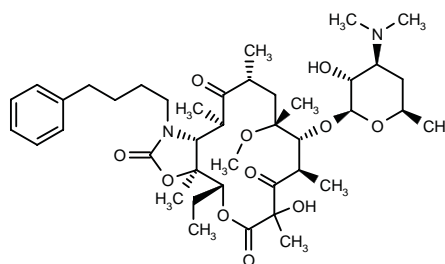
SOURCES – Merck & Co.; Princeton University, Princeton, NJ (US).

REFERENCES

1. Kim, R.M. et al. (Merck & Co., Inc.; Princeton University) *Glycopeptide antibacterial cpds., compsns. containing same and methods of using same*. WO 0069893.

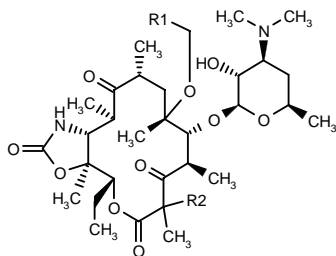
297700

11-Deoxy-3-des(hexopyranosyloxy)-2-hydroxy-6-*O*-methyl-3-oxo-11-[N-(4-phenylbutyl)amino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C41 H64 N2 O11; Mol wt: 760.9596

ACTION – Semisynthetic macrolide that demonstrated antibacterial activity against several strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Streptococcus pyogenes*, *Micrococcus luteus*, *Escherichia coli* and *Candida albicans*, among others. Other exemplified C2-modified erythromycin derivatives include the following:



Compound	R1	R2	Formula
297711	H	CH2CH=CHPh	C ₄₀ H ₆₀ N ₂ O ₁₀
297715	CH(OH)CH2OH	OH	C ₃₃ H ₅₆ N ₂ O ₁₃
297717	(E)-3-quinoliny-CH=CH	allyl	C ₄₅ H ₆₃ N ₃ O ₁₀
297720	(E)-3-quinoliny-CH=CH	OH	C ₄₂ H ₅₉ N ₃ O ₁₁
297722	ethynyl	CH2CH=CHPh	C ₄₂ H ₆₀ N ₂ O ₁₀

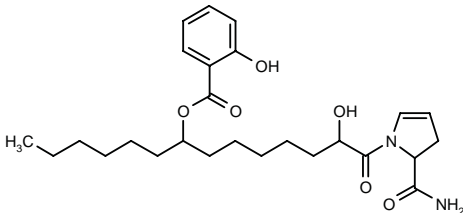
SOURCE – Abbott.

REFERENCES

1. Ma, Z. et al. (Abbott Laboratories Inc.) *C-2 modified erythromycin derivs.* WO 0069875.

299180

2-Hydroxybenzoic acid 8-(2-carbamoyl-2,3-dihydro-1*H*-pyrrol-1-yl)-1-hexyl-7-hydroxy-8-oxooctyl ester



C26 H38 N2 O6; Mol wt: 474.5942

ACTION – Aralkyl-peptide antibiotic produced by eubacterial fermentation of a *Pseudomonas* sp. that showed a broad spectrum of activity against Gram-positive and Gram-negative bacteria. It was active against resistant *Pseudomonas aeruginosa* spp. (MIC = 0.12-64 µg/ml), *Vibrio cholerae* and *Vibrio parahaemolyticus* (MIC = 32-128 µg/ml), *Acinetobacter calcoaceticus* (MIC = 32-128 µg/ml), *Stenotrophomonas maltophilia* (MIC = 64 µg/ml), *Staphylococcus aureus* and *Staphylococcus hemolyticus* (MIC = 32-64 µg/ml), *Pediococcus* spp. (MIC = 32 µg/ml) and *Streptococcus pyogenes* and *Streptococcus pneumoniae* (MIC = 32 µg/ml).

SOURCE – Merck & Co.

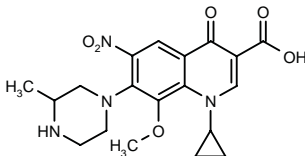
REFERENCES

1. Bernard-King, A.M. et al. (Merck & Co., Inc.) *Antibiotic cpd.* WO 0078308.

ANTIBACTERIAL DRUGS

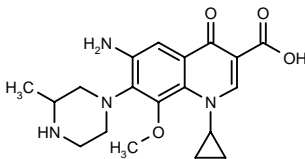
297215

1-Cyclopropyl-8-methoxy-7-(3-methylpiperazin-1-yl)-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C19 H22 N4 O6; Mol wt: 402.4048

ACTION – Antibacterial agent, a representative compound from a series of quinolone carboxylate derivatives. Another exemplified compound is:



297216: C19 H24 N4 O4

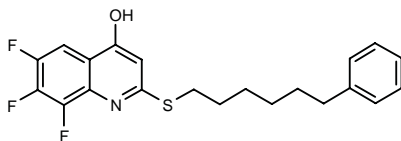
SOURCE – Kyorin.

REFERENCES

1. Asahina, Y. (Kyorin Pharmaceutical Co., Ltd.) *Novel quinolone carboxylate derivs.* JP 2000256325.

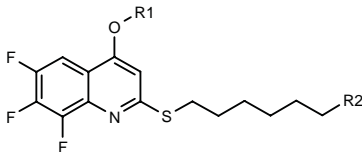
297670

6,7,8-Trifluoro-2-(6-phenylhexylsulfanyl)quinolin-4-ol



C21 H20 F3 N O S; Mol wt: 391.4550

ACTION – Antibacterial quinoline that was active against methicillin-resistant *Staphylococcus aureus* HPC1360, HPC1336 and HPC423, and *Staphylococcus epidermidis* HPC10019 and HPC1728. Other 2-mercaptoquinoline derivatives from this series are:



Compound	R1	R2	Formula
297671	H	Pr	C ₁₈ H ₂₂ F ₃ NOS
297672	Ac	H	C ₁₇ H ₁₈ F ₃ NO ₂ S

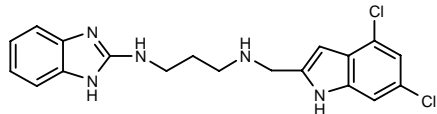
SOURCE – Hokuriku.

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1. Kako, N. et al. (Hokuriku Seiyaku Co., Ltd.) 2-Mercaptoquinoline derivs. JP 2000302760.

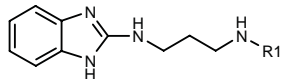
297860

N-(1H-Benzimidazol-2-yl)-N'-(4,6-dichloro-1H-indol-2-ylmethyl)propane-1,3-diamine



C19 H19 Cl2 N5; Mol wt: 388.3001

ACTION – Antibacterial agent, a potent inhibitor of *Staphylococcus aureus* methionyl-tRNA synthetase (MRS; methionine–tRNA ligase), giving an IC₅₀ value in the range < 3-700 nM against recombinant MRS and showing high selectivity with respect to mammalian enzyme (no inhibition of rat MRS up to 1 μM). Compound exhibited MIC values of 1 μg/ml or less against *S. aureus*, *Streptococcus pneumoniae* and *Enterococcus faecalis* and in the range 1-32 μg/ml against *Moraxella catarrhalis*, and was further shown to be active also against *Haemophilus influenzae*. Other specifically claimed compounds from this series of benzimidazole derivatives are:



Compound	R1	Formula
297861	6,8-(Br)2-1,2,3,4-tetrahydro-4-quinolyl	C ₁₉ H ₂₁ Br ₂ N ₅
297862	6-Et-8-I-1,2,3,4-tetrahydro-4-quinolyl	C ₂₁ H ₂₆ IN ₅
297863	4,6-(Cl)2-1-(CH2CH2OH)-2-indolyl-CH2	C ₂₁ H ₂₃ Cl ₂ N ₅ O
297864	2-EtO-3-Me-5-I-PhCH2	C ₂₀ H ₂₅ IN ₄ O
297865	4-CF3-6-MeO-2-indolyl-CH2	C ₂₁ H ₂₂ F ₃ N ₅ O

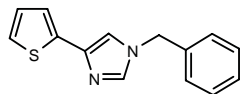
SOURCE – GlaxoSmithKline.

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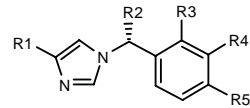
297868

1-Benzyl-4-(2-thienyl)-1H-imidazole

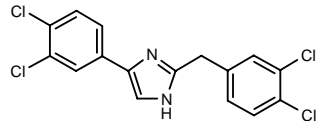


C14 H12 N2 S; Mol wt: 240.3288

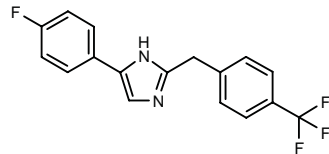
ACTION – Antibacterial agent that acts by inhibiting Fab I (previously known as EnvM), an enzyme that is essential to bacterial fatty acid biosynthesis. Compound may also be of use as an antifungal agent. Other specifically claimed compounds from this series of imidazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
297869	2-thienyl	H	H	H	Cl	C ₁₄ H ₁₁ ClN ₂ S
297870	3-thienyl	H	H	H	OMe	C ₁₅ H ₁₄ N ₂ OS
297871	4-N(Me)2-Ph	H	H	H	OH	C ₁₈ H ₁₉ N ₃ O
297872	4-i-PrO-Ph	H	H	H	NH2	C ₁₉ H ₂₁ N ₃ O
297874	2-F-3-CF3-Ph	H	H	CF3	Cl	C ₁₈ H ₁₀ ClF ₇ N ₂
297877	3-thienyl	H	NO2	H	H	C ₁₄ H ₁₁ N ₃ O ₂ S
297878	3-thienyl	Me	H	H	H	C ₁₅ H ₁₄ N ₂ S



297875: C16 H10 Cl4 N2



297876: C17 H12 F4 N2

SOURCE – GlaxoSmithKline.

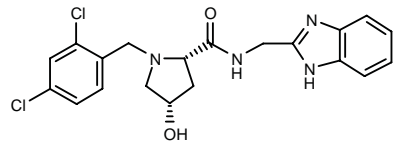
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CB-130900

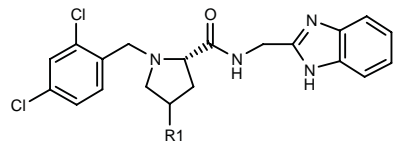
296879

N¹-(1H-Benzimidazol-2-ylmethyl)-N²-(2,4-dichlorobenzyl)-4(S)-hydroxy-L-prolinamide



C20 H20 Cl2 N4 O2; Mol wt: 419.3100

ACTION – Antimicrobial agent, a tRNA synthetase inhibitor that is active against a broad spectrum of bacteria and fungi. Other exemplified prolines include the following:



Compound	R1	Formula
CB-130901 [296880]	(R)-OH	C ₂₀ H ₂₀ Cl ₂ N ₄ O ₂
CB-126881 [296881]	H	C ₂₀ H ₂₀ Cl ₂ N ₄ O
CB-127006 [296883]	OH	C ₂₀ H ₂₀ Cl ₂ N ₄ O ₂

SOURCES – Cubist; Merck & Co.

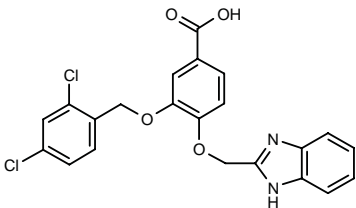
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1. Leeman, A.H. et al. (Merck & Co., Inc.;Cubist Pharmaceuticals, Inc.) *Novel prolines as antimicrobial agents*. WO 0066119.

CB-130913

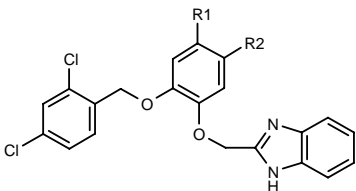
296884

4-(1*H*-Benzimidazol-2-ylmethoxy)-3-(2,4-dichlorobenzyl-oxy)benzoic acid



C22 H16 Cl2 N2 O4; Mol wt: 443.2844

ACTION – Antimicrobial agent, a tRNA synthetase inhibitor that is active against a broad spectrum of bacteria and fungi. Other exemplified catechols include the following:



Compound	R1	R2	Formula
CB-126898 [296885]	H	CO2H	C ₂₂ H ₁₆ Cl ₂ N ₂ O ₄
CB-130920 [296886]	H	CONHCH2CO2H	C ₂₄ H ₁₉ Cl ₂ N ₃ O ₅
CB-130927 [296887]	H	CO-L-Asp-OH	C ₂₆ H ₂₁ Cl ₂ N ₃ O ₇
CB-130969 [296888]	CONHCH2CO2H	H	C ₂₄ H ₁₉ Cl ₂ N ₃ O ₅
CB-130970 [296890]	CO-L-Ser-OH	H	C ₂₆ H ₂₁ Cl ₂ N ₃ O ₆
CB-130971 [296892]	CONHSO2Me	H	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₅ S

SOURCES – Cubist; Merck & Co.

REFERENCES

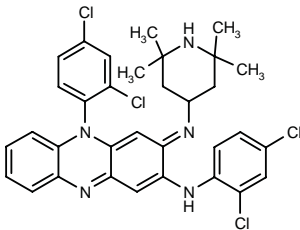
1. Leeman, A.H. et al. (Merck & Co., Inc.;Cubist Pharmaceuticals, Inc.) *Novel catechols as antimicrobial agents*. WO 0066120.

ANTIMYCOBACTERIAL AGENTS

B-4128

299655

N,5-Bis(2,4-dichlorophenyl)-3-(2,2,6,6-tetramethyl-piperidin-4-ylimino)-3,5-dihydrophenazin-2-amine



C33 H31 Cl4 N5; Mol wt: 639.4549

ACTION – Antimycobacterial agent, a tetramethylpiperidyl-substituted phenazine designed to enhance the antimycobacterial activity and reduce the adverse effects of clofazimine. Compound almost completely inhibited the growth of *Mycobacterium aurum* A⁺ at 0.6 and 1.25 mg/l and it significantly inhibited the growth of *Mycobacterium tuberculosis* H37Ra at 0.6 mg/l, with a potency approximately 5-10-fold higher than clofazimine. Compound exhibited membrane-directed antimycobacterial properties, as demonstrated by an immediate and concentration-dependent increase in phospholipase A₂ (PLA₂) activity and inhibition of K⁺ uptake (measured as ⁸⁶Rb⁺ uptake) in *M. aurum*, followed by an increase in Ca²⁺ and a reduction in mycobacterial ATP.

SOURCES – Adcock Ingram; University College Dublin, Dublin (IE); University of Pretoria, Pretoria (ZA).

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1. Medlen, C.E. et al. (Adcock Ingram Ltd.;University of Pretoria) *Use of riminophenazine for treating MDR resistance*. EP 0676201, US 5763443.

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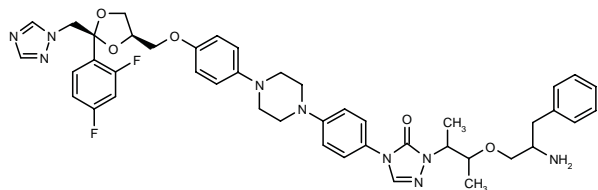
5. van Rensburg, C.E. et al. *In vitro investigation of the antimicrobial activities of novel tetramethylpiperidine-substituted phenazines against Mycobacterium tuberculosis*. Chemotherapy 2000, 46(1): 43.

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ANTIFUNGAL AGENTS

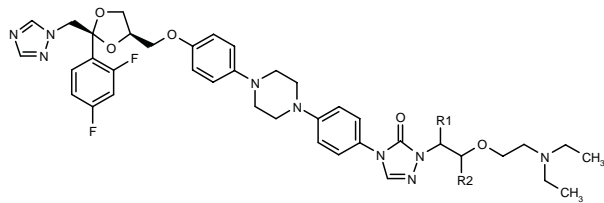
296721

1-[2-(2-Amino-3-phenylpropoxy)-1-methylpropyl]-4-[4-[4-[(2*S*,4*R*)-2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl]piperazin-1-yl]phenyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one



C44 H49 F2 N9 O5; Mol wt: 821.9251

ACTION – Antifungal agent with potent and broad-spectrum activity, as demonstrated *in vitro* against *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida kefyr*, *Candida tropicalis*, *Microsporum canis*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans* and *Aspergillus fumigatus* by MIC values of < 0.01, 1, 1, < 0.01, < 0.01, 0.1, 1, 0.1, 1, 0.1 and 1 μ M, respectively. Compound exhibits good water solubility (> 7.09 mg/ml at pH 3.65). Other exemplified compounds from this series of ether derivatives include the following:



Compound	R1	R2	Formula
296722	Me	Me	C ₄₁ H ₅₁ F ₂ N ₉ O ₅
296723	H	H	C ₃₉ H ₄₇ F ₂ N ₉ O ₅
296724	Et	H	C ₄₁ H ₅₁ F ₂ N ₉ O ₅

SOURCE – Janssen.

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CASPOFUNGIN ACETATE

Prop INN, USAN

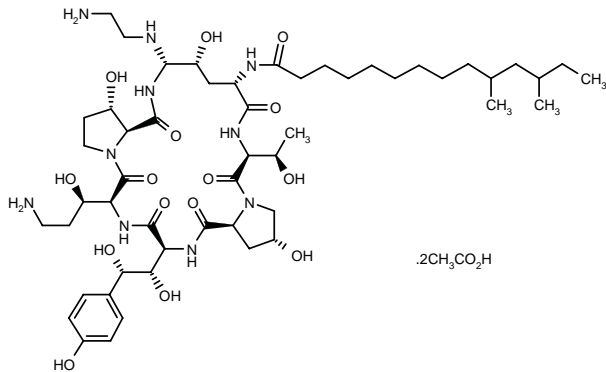
236886

(3*S*,6*S*,9*S*,11*R*,15*S*,18*S*,20*R*,21*S*,24*S*,25*S*)-21-(2-Aminoethylamino)-3-[3-amino-1(*R*)-hydroxypropyl]-6-[1(*S*),2(*S*)-dihydroxy-2-(4-hydroxyphenyl)ethyl]-18-(10,12-dimethyltetradecanamido)-11,20,25-trihydroxy-15-[1(*R*)-hydroxyethyl]-1,4,7,13,16,22-hexaazatricyclo-[22.3.0.0^{9,13}]heptacosane-2,5,8,14,17,23-hexaone diacetate

(2*R*,6*S*,9*S*,11*R*,12*S*,14*aS*,15*S*,20*S*,23*S*,25*aS*)-12-(2-Aminoethylamino)-20-[3-amino-1(*R*)-hydroxypropyl]-23-[1(*S*),2(*S*)-dihydroxy-2-(4-hydroxyphenyl)ethyl]-9-(10,12-dimethyltetradecanamido)-2,11,15-trihydroxy-6-[1(*R*)-hydroxyethyl]perhydrodipyrrolo[2,1-*c*:2',1'-/]-[1,4,7,10,13,16]hexaazacycloheptacosine-5,8,14,19,22,25-hexaone diacetate

1-[4*R*,5*S*]-5-(2-Aminoethylamino)-*N*²-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[3(*R*)-hydroxy-L-ornithine]-pneumocandin B₀ diacetate

L-743872⁺
MK-0991
MK-991



C52 H88 N10 O15 . 2 C2 H4 O2; Mol wt: 1213.4250

ACTION – Semisynthetic echinocandin that inhibits the synthesis of fungal cell wall β -(1,3)-glucan.

INDICATIONS – Treatment of invasive aspergillosis in patients who do not respond to or cannot tolerate other antifungal therapies, i.e., amphotericin B, lipid formulations of amphotericin B and/or itraconazole.

PRESENTATION – Vials of powder/cake for infusion, 50 and 70 mg.

PROPRIETARY NAME – *Cancidas* (US).

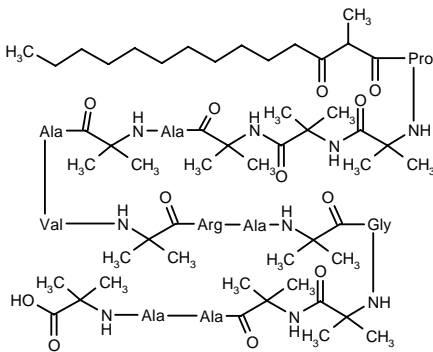
SOURCE – Merck & Co.

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2. Arikan, S. et al. *In vitro susceptibility testing methods for caspofungin (CAS) against Aspergillus (ASP) and Fusarium (FUS) isolates*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst J160.

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Sch-466456 [299163]: C84 H147 N21 O21

SOURCE – Schering-Plough.

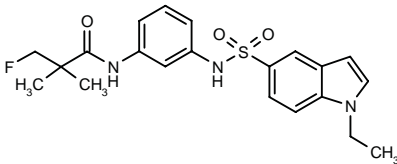
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ANTIVIRAL DRUGS

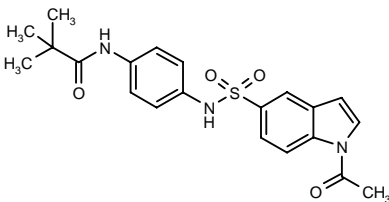
296639

N-[3-(1-Ethyl-1*H*-indol-5-ylsulfonamido)phenyl]-3-fluoro-2,2-dimethylpropionamide



C21 H24 F N3 O3 S; Mol wt: 417.5026

ACTION – Antiviral agent for the treatment of cytomegalovirus (CMV) infections, with an IC₅₀ of 0.055 μM against HCMV in HELF cells and much lower cytotoxicity (CC₅₀ = 15.6 μM) in uninfected cells. Another exemplified compound from this series of substituted indole sulfonamides is:



296643: C21 H23 N3 O4 S

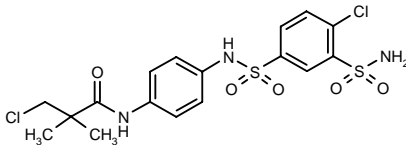
SOURCE – Bayer.

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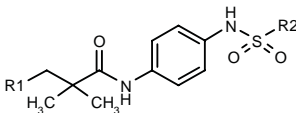
297164

N-[4-(4-Chloro-3-sulfamoylphenylsulfonamido)phenyl]-3-chloro-2,2-dimethylpropionamide



C17 H19 Cl2 N3 O5 S2; Mol wt: 480.3911

ACTION – Antiviral agent active against human cytomegalovirus (HCMV), as demonstrated by an IC₅₀ value of 0.019 μM against HCMV in HELF cells. Other exemplified compounds from this series of bis-sulfonamide derivatives include the following:



Compound	R1	R2	Formula
297165	Cl	5-(4-morpholinyl-SO2)-1-Naph	C ₂₅ H ₂₈ ClN ₃ O ₆ S ₂
297166	Cl	5-(perhydro-1-azepinyl-SO2)-1-Naph	C ₂₇ H ₃₂ ClN ₃ O ₆ S ₂
297167	Cl	5-(2-OH-PhNHSO2)-1-Naph	C ₂₇ H ₂₆ ClN ₃ O ₆ S ₂
297192	F	4-Cl-3-(NH2SO2)-Ph	C ₁₇ H ₁₉ ClFN ₃ O ₅ S ₂
297193	F	3-[N(Me)2SO2]-Ph	C ₁₉ H ₂₄ FN ₃ O ₅ S ₂
297194	F	3-(4-Et-1-Piz-SO2)-Ph	C ₂₃ H ₃₁ FN ₃ O ₅ S ₂
297195	F	5-(4-thiomorpholinyl-SO2)-1-Naph	C ₂₅ H ₂₈ FN ₃ O ₅ S ₃

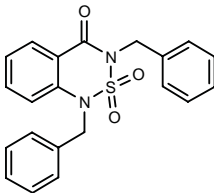
SOURCE – Bayer.

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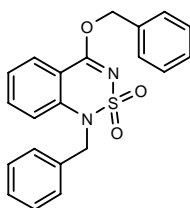
297316

1,3-Dibenzyl-3,4-dihydro-1*H*-2,1,3-benzothiadiazin-4-one 2,2-dioxide



C21 H18 N2 O3 S; Mol wt: 378.4502

ACTION – Antiviral agent for the treatment of infections caused by cytomegalovirus (CMV) and varicella-zoster virus (VZV) that is reported to exhibit comparable antiviral activity to ganciclovir while having a different mechanism of action, which makes it particularly suitable for the treatment of ganciclovir-resistant strains. Another exemplified compound from this series of fused 1,2,6-thiadiazine-2,2-dioxide derivatives is:



297317: C₂₁ H₁₈ N₂ O₃ S

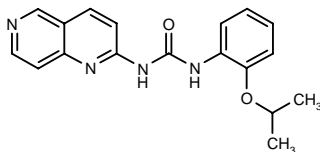
SOURCE – CSIC, Madrid (ES).

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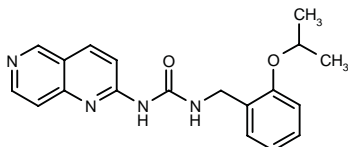
299187

N-(2-Isopropoxyphenyl)-*N'*-(1,6-naphthyridin-2-yl)urea



C₁₈ H₁₈ N₄ O₂; Mol wt: 322.3662

ACTION – Antiviral agent active against human cytomegalovirus (IC₅₀ = 0.03 µg/ml in human foreskin fibroblast Hs68 cells), with low cytotoxicity in uninfected cells (CC₅₀ = 30.2 µg/ml). Another related 1,6-naphthyridine-2-carboxylic acid benzylamide is:



299182: C₁₉ H₂₀ N₄ O₂

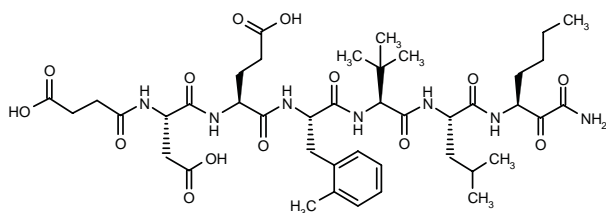
SOURCE – BioChem Pharma.

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1. Bedard, J. et al. (BioChem Pharma Inc.) *Antiviral cpds.* EP 1037633, WO 9929318.
2. Jin, H. et al. (BioChem Pharma Inc.) *Naphthyridine derivs. and their analogues inhibiting cytomegalovirus.* EP 0984967, US 5945431, WO 9734894.
3. Chan, L. et al. *Design and synthesis of new potent human cytomegalovirus (HCMV) inhibitors based on internally hydrogen-bonded 1,6-naphthyridines.* Bioorg Med Chem Lett 2001, 11(2): 103.

299551

N-(3-Carboxypropionyl)-L-aspartyl-L-glutamyl-(2-methyl)-L-phenylalanyl-(3-methyl)-L-valyl-*N*¹-[1(*S*)-(2-amino-2-oxoacetyl)pentyl]-L-leucinamide



C₄₂ H₆₃ N₇ O₁₄; Mol wt: 889.9947

ACTION – Hepatitis C virus NS3-4A protease inhibitor (IC₅₀ = 11 nM) with high selectivity relative to other human serine proteases including elastase, chymotrypsin and trypsin (IC₅₀ = 12,000, 300 and > 200,000 nM, respectively). Potentially useful for the treatment of hepatitis C infections.

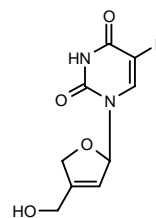
SOURCE – Roche.

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3. Wilson, F.X. et al. *Design and synthesis of hepatitis C NS3 proteinase inhibitors.* J Hepatol 2001, 34(Suppl. 1): 116.

300078

5-Fluoro-1-[4-(hydroxymethyl)-2,5-dihydro-2-furanyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione



C₉ H₉ F N₂ O₄; Mol wt: 228.1781

ACTION – Antiviral agent active against human cytomegalovirus (EC₅₀ = 6.9 and 2.81 µg/ml against AD-169 and Davis strains, respectively) but devoid of activity against HIV-1, herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and cytotoxicity in uninfected human embryonic lung fibroblast HEL cells (CC₅₀ > 100 µg/ml). Compound was 9-13-fold more active than foscarnet but approximately 5-fold less active than ganciclovir.

SOURCES – Ewha Womans University, Seoul (KR); Korea Research Institute of Chemical Technology, Taejeon (KR); Yonsei University, Seoul (KR).

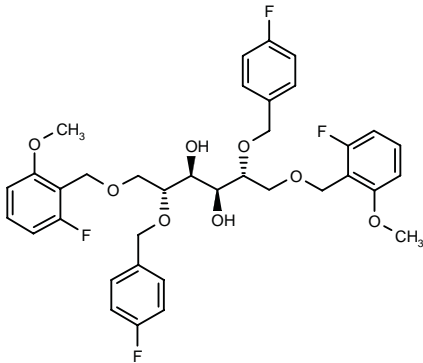
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AIDS MEDICINES

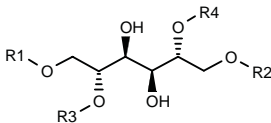
296746

1,6-Di-*O*-(2-fluoro-6-methoxybenzyl)-2,5-di-*O*-(4-fluorobenzyl)-D-mannitol

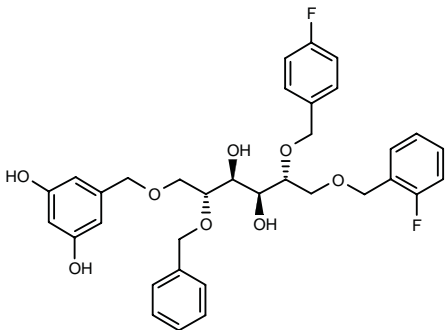


C36 H38 F4 O8; Mol wt: 674.6802

ACTION – Antiviral agent for AIDS, an HIV aspartyl protease inhibitor (K_i = 0.12 μ M against recombinant HIV-1 protease). Other exemplified compounds from this series of D-mannitol derivatives include the following:



Compound	R1=R2	R3	R4	Formula
296747	CH2Ph	CH2Ph	CH2Ph	C ₃₄ H ₃₈ O ₆
296748	2,6-(F)2-PhCH2	CH2Ph	CH2Ph	C ₃₄ H ₃₄ F ₄ O ₆
296749	CH2Ph	3-Pyr-CH2	3-Pyr-CH2	C ₃₂ H ₃₆ N ₂ O ₆
296750	2-F-PhCH2	4-F-PhCH2	4-F-PhCH2	C ₃₄ H ₃₄ F ₄ O ₆
296751	2-thienyl	4-F-Ph	4-F-Ph	C ₂₆ H ₂₄ F ₂ O ₆ S ₂
296752	Ph	4-F-Ph	2-thienyl	C ₂₈ H ₂₇ FO ₆ S
296753	2-F-Ph	4-F-Ph	2-thienyl	C ₂₈ H ₂₅ F ₃ O ₆ S
297228	2-F-4-OH-PhCH2	4-F-PhCH2	4-F-PhCH2	C ₃₄ H ₃₄ F ₄ O ₈
297229	2-F-PhCH2	2-OH-PhCH2	4-F-PhCH2	C ₃₄ H ₃₅ F ₃ O ₇



297230: C34 H36 F2 O8

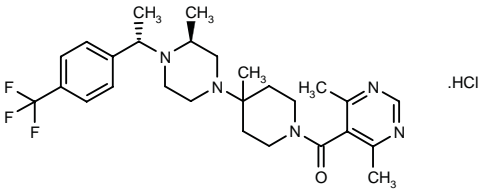
SOURCE – Pharmacor.

REFERENCES

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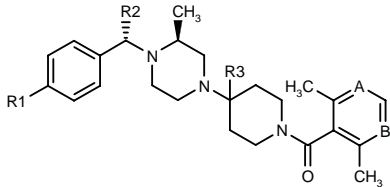
296783

1-(4,6-Dimethylpyrimidin-5-yl)-1-[4-methyl-4-[3(*S*)-methyl-4-[1(*S*)-[4-(trifluoromethyl)phenyl]ethyl]piperazin-1-yl]piperidin-1-yl]methanone hydrochloride



C27 H36 F3 N5 O . HCl; Mol wt: 540.0703

ACTION – Chemokine CCR5 receptor antagonist with potential for the treatment of HIV infection, organ transplant rejection, graft-versus-host disease, arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies and multiple sclerosis. *In vitro*, compound exhibited a K_i value of 2.95 nM for inhibition of [³H]-RANTES binding in NIH 3T3 cells expressing the human CCR5 receptor. Other exemplified compounds from this series of piperazine derivatives include the following:



Compound	R1	R2	R3	A	B	Formula
296784	H	Ph	Me	N	CH	C ₃₂ H ₄₀ N ₄ O
296785	OCF3	Et	H	N	N	C ₂₇ H ₃₆ F ₃ N ₅ O ₂
296786	I	Me	H	CH	CH	C ₂₇ H ₃₆ IN ₃ O
296787	Ph	Me	H	CH	CH	C ₃₃ H ₄₁ N ₃ O

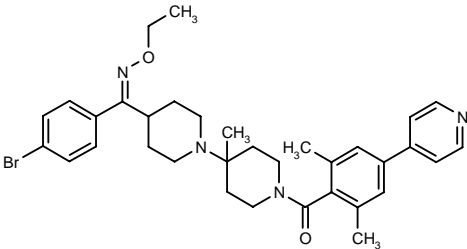
SOURCE – Schering-Plough.

REFERENCES

1. Baroudy, B.M. et al. (Schering Corp.) *Piperazine derivs. useful as CCR5 antagonists*. WO 0066558.

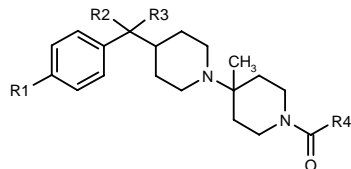
296788

1-(4-Bromophenyl)-1-[1-[1-[2,6-dimethyl-4-(4-pyridin-yl)benzoyl]-4-methylpiperidin-4-yl]piperidin-4-yl]-methanone *O*-ethyloxime



C34 H41 Br N4 O2; Mol wt: 617.6279

ACTION – Chemokine CCR5 receptor antagonist with potential for the treatment of HIV infection, organ transplant rejection, graft-versus-host disease, arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies and multiple sclerosis. *In vitro*, compound exhibited a K_i value of 0.1 nM for inhibition of [^3H]-RANTES binding in NIH 3T3 cells expressing the human CCR5 receptor. Other exemplified compounds from this series of piperidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
296789	CF3	2-Pyr-O	H	3,5-(Cl)2-4-Pyr	C ₃₀ H ₃₁ Cl ₂ F ₃ N ₄ O ₂
296790	Br	2-Pyr-O	H	2,4-(Me)2-3-Pyr	C ₃₁ H ₃₇ BrN ₄ O ₂
296791	Br	2-Pyr-O	H	4,6-(Me)2-5-pyrimidinyl	C ₃₀ H ₃₆ BrN ₅ O ₂
296792	Br	-N(OEt)-		3,5-(Cl)2-4-Pyr	C ₂₆ H ₃₁ BrCl ₂ N ₄ O ₂
296793	Br	-N(OEt)-		3,5-(Br)2-4-Pyr	C ₂₆ H ₃₁ Br ₃ N ₄ O ₂
296794	CF3	N(OMe)		3,5-(Cl)2-4-Pyr	C ₂₆ H ₂₉ Cl ₂ F ₃ N ₄ O ₂

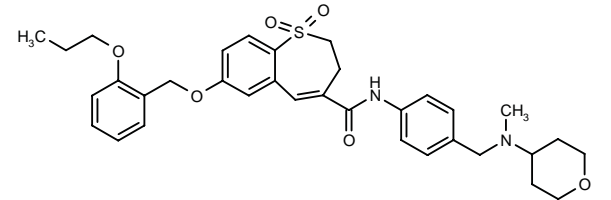
SOURCE – Schering-Plough.

REFERENCES

1. Baroudy, B.M. et al. (Schering Corp.) *Piperidine derivs. useful as CCR5 antagonists*. WO 0066559.

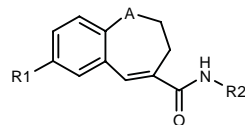
297497

N-[4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)amino-methyl]phenyl]-7-(2-propoxybenzyloxy)-2,3-dihydro-1-benzothiepin-4-carboxamide 1,1-dioxide



C34 H40 N2 O6 S; Mol wt: 604.7640

ACTION – Anti-HIV agent, a chemokine CCR5 antagonist shown to produce 98% inhibition of CCR5 binding to human receptors expressed in CHO cells. Other exemplified cyclic compounds include the following:



Compound	R1	R2	A	Formula
297498	4-PrO-Ph-CH2CH2O	4-[4-THP-N(Me)CH2]-Ph	-SO2-	C ₃₅ H ₄₂ N ₂ O ₆ S
297500	3-PrO-PhCH2O	4-[4-THP-N(Me)CH2]-Ph	-SO2-	C ₃₄ H ₄₀ N ₂ O ₆ S
297503	4-Me-Ph	1-(4-THP)-4-Pip	-SO2-	C ₂₈ H ₃₄ N ₂ O ₄ S
297504	4-Me-Ph	4-(4,5-dihydro-2-imidazolyl-CH2)-Ph	-O-	C ₂₈ H ₂₇ N ₃ O ₂
297505	4-PrO-PhCH2O	4-[4-THP-N(Me)CH2]-Ph	-SO2-	C ₃₄ H ₄₀ N ₂ O ₆ S
297506	4-(PrOCH2CH2O)-PhCH2O	4-[4-THP-N(Me)CH2]-Ph	-SO2-	C ₃₆ H ₄₄ N ₂ O ₇ S
297507	4-PrO-Ph(CH2)3O	4-[4-THP-N(Me)CH2]-Ph	-SO2-	C ₃₆ H ₄₄ N ₂ O ₆ S

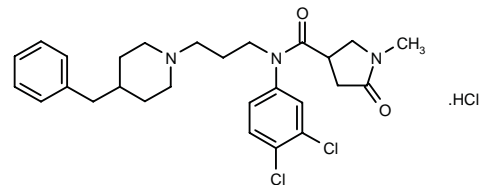
SOURCE – Takeda.

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1. Shiraishi, M. et al. (Takeda Chemical Industries, Ltd.) *Cyclic cpds. and uses thereof*. JP 2001026586, WO 0068203.

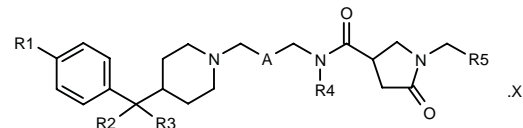
297591

N-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*-(3,4-dichlorophenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide hydrochloride

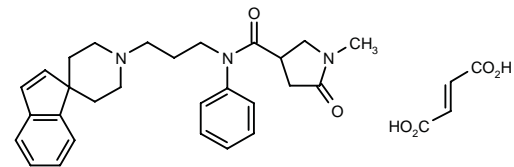


C27 H33 Cl2 N3 O2 . HCl; Mol wt: 538.9436

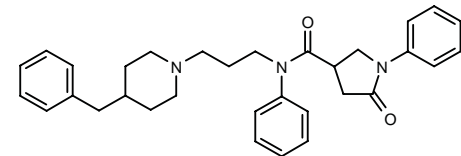
ACTION – Chemokine CCR5 receptor antagonist shown to produce 95% inhibition of CCR5 binding in CHO cells expressing the human receptor at 1.0 μM . The compound is useful for the treatment of HIV infection, particularly AIDS. Other exemplified cyclic amide compounds include the following:



Compound	R1	R2	R3	R4	R5	A	X	Formula
297593	H	H	H	Ph	H	-CH2-	HCl	C ₂₇ H ₃₅ N ₃ O ₂ .HCl
297595	F	-O-		Ph	H	-CH2-		C ₂₇ H ₃₂ FN ₃ O ₃
297597	F	-O-		Ph	H	-(CH2)2-		C ₂₈ H ₃₄ FN ₃ O ₃
297598	H	H	H	3-Cl-Ph	H	-CH2-	HCl	C ₂₇ H ₃₄ ClN ₃ O ₂ .HCl
297599	H	H	H	Ph	Ph	-CH2-		C ₃₃ H ₃₉ N ₃ O ₂
297601	H	H	H	CH2Ph	H	-CH2-		C ₂₈ H ₃₇ N ₃ O ₂
297602	H	H	H	Ph	2-Cl-Ph	-CH2-		C ₃₃ H ₃₆ ClN ₃ O ₂
297603	F	H	H	3,4-(Cl)2-Ph	H	-CH2-	HCl	C ₂₇ H ₃₂ Cl ₂ FN ₃ O ₂ .HCl
297604	H	H	H	Ph	CF3	-CH2-		C ₂₈ H ₃₄ F ₃ N ₃ O ₂



297594: C28 H33 N3 O2 . C4 H4 O4



297600: C32 H37 N3 O2

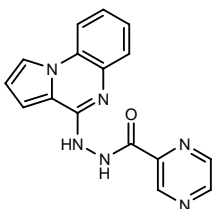
SOURCE – Takeda.

REFERENCES

1. Ishihara, Y. et al. (Takeda Chemical Industries, Ltd.) *Cyclic amide cpds., process for the preparation of the same and uses thereof*. JP 2001011073, WO 0066551.

298906

N'-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)pyrazine-2-carbohydrazide



C16 H12 N6 O; Mol wt: 304.3118

ACTION – Broad-spectrum anti-HIV agent, a potent non-nucleoside HIV-1 reverse transcriptase (RT) inhibitor with a K_i value of 0.19 μ M against wild-type enzyme and 0.3, 2.5 and 0.8 μ M, respectively, against mutant enzymes containing the single amino acid substitutions L100I, Y181I and V106A. Compound was also active against a Y188L RT mutation that appeared in patients treated with both nevirapine and zidovudine. It inhibited syncytium formation in C8166 cells infected with wild-type HIV-1_{IIIB} with a potency equal to that of zidovudine (IC_{50} = 0.4 μ M) and HIV-1 p24 antigen production in monocytes/macrophages infected with HTLV-III BA-L, a laboratory-adapted monocytotropic strain; low cytotoxic activity was seen against uninfected C8166 cells (IC_{50} = 18 μ M), as well as against murine 3T3 fibroblasts, human Daudi and murine NSO cell lines (IC_{50} = 0.88, 0.86, and 0.87 mM, respectively). Compound was able to potentiate the antiviral affect of zidovudine in HIV-1_{IIIB}-infected C8166 cells, giving an EC_{50} with zidovudine of 15 nM compared to an EC_{50} of 450 nM when used alone. Preliminary pharmacokinetic studies in mice demonstrated that compound was rapidly absorbed after oral administration, with mean plasma C_{max} of 6.5 nmol/ml at 30 min (after the dose of 20 mg/kg), and that it crossed the blood–brain barrier, achieving peak brain levels at approximately the same time as those in plasma after either i.p. or oral administration.

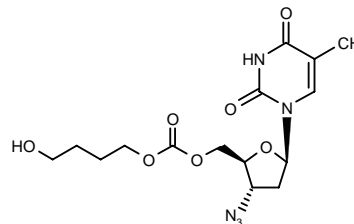
SOURCE – Istituto di Ricerche Farmacologiche Mario Negri, Milano (IT).

REFERENCES

1. Campiani, G. et al. *Quinoxalinyethylpyridylthioureas (QXPTs) as potent non-nucleoside HIV-1 reverse transcriptase (RT) inhibitors. Further SAR studies and identification of a novel orally bioavailable hydrazine-based antiviral agent*. J Med Chem 2001, 44(3): 305.

299221

3'-Azido-3'-deoxy-5'-O-(4-hydroxybutyloxycarbonyl)-thymidine



C15 H21 N5 O7; Mol wt: 383.3589

ACTION – Anti-HIV agent, a carbonate prodrug of zidovudine (AZT) with enhanced anti-HIV-1 activity in acutely infected MT-4 cells (EC_{50} = 0.5 and 25 nM, respectively, for inhibition of HIV-1 cytopathicity) and peripheral blood mononuclear cells (EC_{50} = 0.78 and 7.5 nM, respectively, for inhibition of HIV-1 replication). Compound exhibited approximately 2-4-fold less cytotoxicity than AZT in uninfected cells. The increased anti-HIV activity of compound may be attributed to its resistance to enzymatic hydrolysis, increased cellular uptake and/or prolonged intracellular release of AZT.

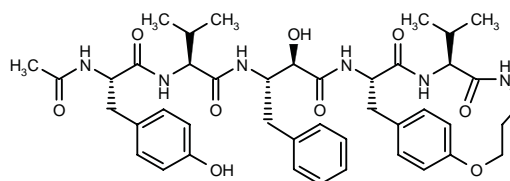
SOURCE – Laphal.

REFERENCES

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2. Vlieghe, P. et al. (Laboratoires Laphal) *Novel esters derived from nucleosides, preparation methods and pharmaceutical compsns. containing them*. FR 2796384, WO 0104134.
3. Vlieghe, P. et al. *New 3'-azido-3'-deoxythymidin-5'-yl O-(ω-hydroxyalkyl) carbonate prodrugs: Synthesis and anti-HIV evaluation*. J Med Chem 2001, 44(5): 777.

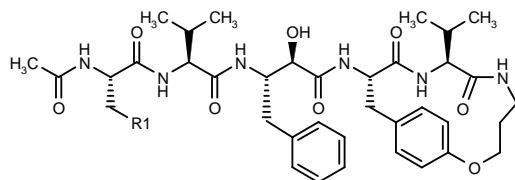
299234

N-Acetyl-L-tyrosyl-*N*¹-[1(*S*)-benzyl-2(*R*)-hydroxy-3-[8(*S*)-isopropyl-7,10-dioxo-2-oxa-6,9-diazabicyclo[11.2.2]heptadeca-1(15),13,16-trien-11(*S*)-ylamino]-3-oxopropyl]-L-valinamide



C43 H56 N6 O9; Mol wt: 800.9484

ACTION – Anti-HIV agent, an inhibitor of HIV and feline immunodeficiency virus (FIV) proteases (IC_{50} = 6 and 27 nM, respectively) that is also active against drug-resistant mutant proteases (IC_{50} = 57 nM against G48V; IC_{50} = 26 nM against V82F; IC_{50} = 11 nM against V82A; IC_{50} = 79 nM against L24I/M46I/F53L/L63P/V77I/V82A). Within this series of norstatin-based protease inhibitors incorporating a conformationally constrained macrocycle, the following are also described:



Compound	R1	Formula
299235	3-indolyl	C ₄₅ H ₅₇ N ₇ O ₈
299236	Ph	C ₄₃ H ₅₆ N ₆ O ₈

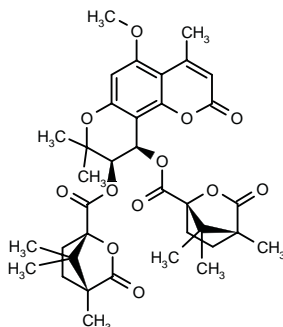
SOURCE – Scripps Research Institute, La Jolla, CA (US).

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1. Mak, C.C. et al. *Design, synthesis, and biological evaluation of HIV/FIV protease inhibitors incorporating a conformationally constrained macrocycle with a small P3' residue*. *Bioorg Med Chem Lett* 2001, 11(2): 219.

300081

(9*R*,10*R*)-5-Methoxy-9,10-[4(*R*),7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1(*S*)-ylcarbonyloxy]-4,8,8-trimethyl-2,8,9,10-tetrahydrobenzo[1,2-*b*:3,4-*b'*]dipyran-2-one



C36 H42 O12; Mol wt: 666.7158

ACTION – Antiviral agent for AIDS with extremely potent inhibitory activity against HIV-1 replication in H9 lymphocytes (EC₅₀ = 7.21 pM) and much more active than zidovudine (EC₅₀ = 45 nM). Compound did not show cytotoxicity in uninfected cells at much higher concentrations (IC₅₀ > 150 μM).

SOURCES – BBI Biotech Research Laboratories; Duke University, Durham, NC (US); University of North Carolina, Chapel Hill, NC (US).

REFERENCES

1. Xie, L. et al. *Anti-AIDS agents. 42. Synthesis and anti-HIV activity of disubstituted (3'*R*,4'*R*)-3',4'-di-*O*-(*S*)-camphanoyl-(+)-cis-khellactone analogues*. *J Med Chem* 2001, 44(5): 664.

F105/2G12/2F5

Triple combination of the three human anti-HIV neutralizing monoclonal antibodies F105, 2G12 and 2F5

299472

ACTION – Triple combination of monoclonal antibodies (MAbs) against SHIV (simian/human immunodeficiency virus) infection, consisting of a human IgG_{1k} monoclonal antibody that recognizes an epitope that overlaps the CD4-binding domain (F105), a human IgG₁ monoclonal antibody that recognizes a gp120 epitope (2G12) and a human monoclonal antibody against gp41 that recognizes the sequence ELDKWA (2F5). The triple combination was highly synergistic against primary HIV isolates and SHIV, and also completely neutralized both viruses in human and monkey peripheral blood mononuclear cells (PBMCs). *In vivo* studies demonstrated that passive immunization with these human MAbs is able to protect primates against both parenteral and mucosal virus exposure. In fact, when the combination was infused into pregnant macaques 5 days before cesarean section and 3 days postpartum, followed by i.v. challenge with SHIV-vpu+ (chimeric simian-human virus encoding the *env* gene of HIV_{IIIIB}), all macaques showed neutralizing levels of antibodies in plasma and none developed infection during 6 months of follow-up, in contrast to all untreated controls. In addition, a neonatal study where the triple MAb combination was given i.v. to dams before cesarean section and to neonates on the day of birth, followed by oral challenge with SHIV-vpu+, showed high levels of neutralizing antibodies in cord blood plasma in all treated infants. In this study, in contrast to the untreated controls, none of the treated infants showed signs of infection for at least 6 months after challenge. Studies on the mechanism of protection indicated that this passive immunotherapy is able to neutralize cell-free virus and kill HIV-infected cells in a non-MHC (major histocompatibility complex)-restricted fashion. Potentially useful for preventing mother-to-infant HIV transmission and as therapeutic postexposure prophylaxis.

SOURCES – Beth Israel Deaconess Medical Center, Boston, MA (US); Dana-Farber Cancer Institute, Boston, MA (US); Harvard Medical School, Boston, MA (US); Tufts University, Boston, MA (US).

REFERENCES

1. Baba, T.W. et al. *Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection*. *Nat Med* 2000, 6(2): 200.
2. Zahr, E.A. et al. *Human anti-HIV-1 monoclonal antibodies that completely prevent SHIV infection of rhesus monkeys have potent, synergistic ADCC activity*. 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 59.

5-HELIX

298602

Protein that binds tightly and specifically to the C-peptide region of gp41

ACTION – Antiviral agent for HIV, a protein designed to bind to a region in the HIV envelope glycoprotein gp41 and prevent HIV fusion to the cell membrane and the consequent infection of the cell. The protein binds specifically and tightly to the C-peptide region of gp41 and displays potent (nanomolar) and broad-spectrum inhibition of HIV-1 variants. It shows high stability and can be made larger to avoid elimination by the kidneys and modified to avoid the body's immune response. Compound may be a useful immunogen for generating anti-HIV antibodies and therefore in the development of vaccines.

SOURCE – Howard Hughes Medical Institute, Chevy Chase, MD (US).

REFERENCES

1. Root, M.J. et al. *Protein design of an HIV-1 entry inhibitor*. 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst LB1.
2. Root, M.J. et al. *Protein design of an HIV-1 entry inhibitor*. Science 2001, 291(5505): 884.

PA-344*

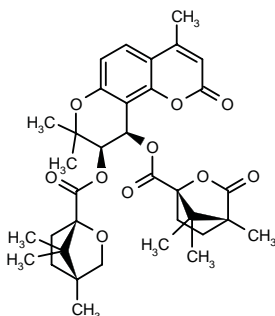
278673

(1*S*,1'*S*,4*R*,4'*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid (9*R*,10*R*)-4,8,8-trimethyl-2-oxo-9,10-dihydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-9,10-diyl ester

(9*R*,10*R*)-4,8,8-Trimethyl-9,10-bis-[4(*R*),7,7-trimethyl-2-oxabicyclo[2,2,1]-heptan-1(*S*)-ylcarbonyloxy]-9,10-dihydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one

3',4'-Di-*O*-[(-)-(*S*)-camphanoyl]-4-methyl-(3'*R*,4'*R*)-*cis*-khellactone

4-Methyldicamphanoylkhellactone
4-MethylDCK



C35 H42 O10; Mol wt: 622.7068

White solid, *m.p.* 264-7 °C; $[\alpha]_D^{20} +8.4^\circ$ (*c* 0.5, CHCl₃).

ACTION – Anti-HIV agent proven to inhibit the replication of various primary HIV-1 isolates at nanomolar concentrations and to have a high selectivity index. Compound also exhibited high synergistic activity when given in combination with zidovudine and certain other approved antiretroviral drugs. It was inactive against HIV-1 reverse transcriptase or protease enzymes and its effect on early phases of the virus replication cycle indicated a novel mechanism of action compared with approved drugs. In rats, compound given i.v. showed peak plasma concentrations about 100-fold higher than the IC₅₀ *in vitro* and a mean terminal half-life of 2.4 h. After oral administration as a suspension, it was not detected in plasma, probably due to its poor solubility in the formulation used. No evidence of toxicity was seen in rats following either i.v. or p.o. dosing.

SOURCES – Biotech Research Laboratories; University of North Carolina, Chapel Hill, NC (US); Panacos.

REFERENCES

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2. Wild, C.T. et al. *The in vitro antiviral activity of the HIV drug candidate 4-methyl dicamphanoyl khellactone*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst 1843.
3. Xie, L. et al. *Anti-AIDS agent 33. Synthesis and anti-HIV activity of mono-methyl substituted 3',4'-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK) analogues*. Bioorg Med Chem Lett 1998, 8(16): 2151.
4. Xie, L. et al. *Anti-AIDS agents. 37.(1) synthesis and structure-activity relationships of (3'*R*,4'*R*)-(+)-*cis*-khellactone derivatives as novel potent anti-HIV agents*. J Med Chem 1999, 42(14): 2662.
5. Boston Biomedica expands license agreement to include anti-HBV candidates. DailyDrugNews.com (Daily Essentials) 2000, July 21.
6. NIH renews HIV drug discovery funding to Panacos collaborators. DailyDrugNews.com (Daily Essentials) 2000, May 2.

*Identified compound **278673** (see **278674**) Drug Data Rep 1999, 021(09): 0811.

QIAN-KUN-NIN

298996

Chinese herbal medicine formulation consisting of Radix Astyagali, Rhizoma Polygonati, Radix Scrophularie, Poria, Herba Artemisiae Scopariae, Rhizoma Coptidis, Fructus Gardeniae, Fructus Forsythiae, Rhizoma Corydalis, Rhizoma Sparganii, Rhizoma Curcumae, Fructus Cnidii, Rhizoma Arisaematis and Galla Chinesis

QKN

ACTION – Chinese herbal medicine formulation consisting of 14 different herbs with antiinfective, anticancer and immunostimulating properties. In a pilot study in HIV-positive subjects, the formulation produced a significant decrease in plasma virus load compared to baseline at both 12 and 24 weeks after starting treatment, and at 4 weeks after terminating treatment. The herbal medicine was also associated with a significant increase in CD4 cell counts at 12 weeks. No adverse events were seen, except mild gastrointestinal disturbances. Another potential indication is the treatment of cardiovascular diseases, as the formulation contains herbs which possess antioxidant properties and was found to reduce oxidative stress and protect chick embryonic cardiomyocytes from death under conditions of mitochondrial electron transport inhibition.

SOURCE – Enwei Institute of Traditional Chinese Medicine, Chengdu (CN).

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TRIZIVIR

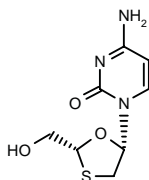
284325

Combination of lamivudine, zidovudine and abacavir sulfate

Lamivudine

184356

(-)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

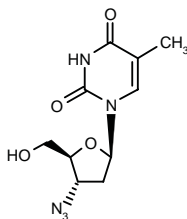


C8 H11 N3 O3 S; Mol wt: 229.2589

Zidovudine

113563

3'-Azido-3'-deoxythymidine

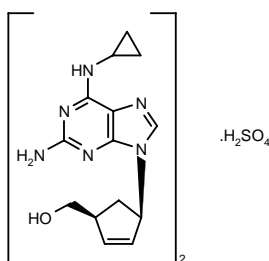


C10 H13 N5 O4; Mol wt: 267.2437

Abacavir sulfate

173602

(1*S*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1)



(C14 H18 N6 O)₂ . H₂ O₄ S; Mol wt: 670.7522

ACTION – Triple combination of the nucleoside anti-retroviral agents abacavir sulfate, lamivudine and zidovudine.

INDICATION – Treatment of HIV-1 infection, alone or in combination with other antiretroviral agents.

PRESENTATION – Tablets containing 300 mg abacavir (as abacavir sulfate), 150 mg lamivudine and 300 mg zidovudine.

PROPRIETARY NAME – Trizivir (EU, US).

SOURCE – GlaxoSmithKline.

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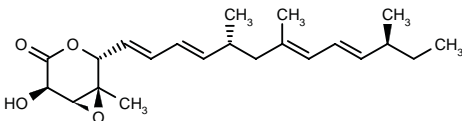
TREATMENT OF HELMINTHIC DISEASES

NAFUREDIN*

262486

(1*R*,2*R*,5*R*,6*R*)-5-Hydroxy-1-methyl-2-[(1*E*,3*E*,5*R*,7*E*,9*E*,11*S*)-5,7,11-trimethyl-1,3,7,9-triadecatetraenyl]-3,7-dioxabicyclo[4.1.0]heptan-4-one

FT-0554



C22 H32 O4; Mol wt: 360.4908

ACTION – Anthelmintic agent produced by *Aspergillus niger* FT-0554 proven to inhibit NADH-fumarate reductase and NADH-rhodoquinonone oxidoreductase (IC₅₀ = 12 nM and 24 nM, respectively) and NADH-ubiquinone oxidoreductase (complex I) from both adult and larval *Ascaris suum* (IC₅₀ = 8 nM and 8.9 nM, respectively). In contrast, the compound exhibited much weaker or no activity against complex II (rhodoquinol-fumarate reductase) from adult *A. suum* (IC₅₀ = 80 μM) and against rat liver enzymes (IC₅₀ = 1 μM or more). In sheep infected with *Haemonchus contortus*, a dose of 2 mg/kg p.o. produced a 90% decrease in egg output after 11 days and complete inhibition of egg output upon retreatment after 1 week. The compound was also highly effective in mice infected with *Hymenolepis nana*. No toxicity was seen in either animal species.

SOURCE – Kitasato Institute, Tokyo (JP).

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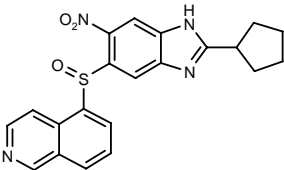
5. Ui, H. et al. *Nafuredin, a novel inhibitor of NADH-fumarate reductase, produced by Aspergillus niger FT-0554*. J Antibiot 2001, 54(3): 234.

*Identified compound **FT-0554** Drug Data Rep 1998, 020(05): 0430, whose chemical structure has been reassigned.

TREATMENT OF SEPTIC SHOCK

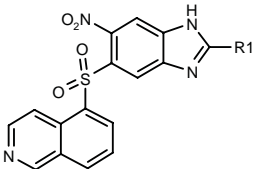
296918

5-(2-Cyclopentyl-6-nitro-1*H*-benzimidazol-5-ylsulfinyl)-isoquinoline



C21 H18 N4 O3 S; Mol wt: 406.4642

ACTION – An inhibitor of TNF-α production (IC₅₀ = 0.12 μM in lipopolysaccharide-stimulated human monocytic THP-1 cells), with potential for the treatment of a broad range of disorders such as septic shock, diabetes, autoimmune diseases, neurodegenerative diseases, rheumatoid arthritis, Crohn's disease, hepatitis, cachexia, bone resorption disorders, myocardial infarction, allergic disorders and adult respiratory distress syndrome. Other exemplified compounds from this series of isoquinoline derivatives include the following:



Compound	R1	Formula
296919	i-Pr	C ₁₉ H ₁₆ N ₄ O ₄ S
296920	t-Bu	C ₂₀ H ₁₈ N ₄ O ₄ S
296922	cyclopentyl	C ₂₁ H ₁₈ N ₄ O ₄ S
296923	cyclopropyl	C ₁₉ H ₁₄ N ₄ O ₄ S

SOURCE – Snow Brand.

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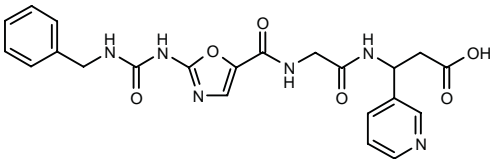
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

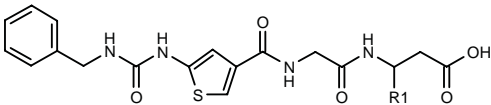
296668

N-[N-[2-(3-Benzylureido)oxazol-5-ylcarbonyl]glycyl]-3-(3-pyridyl)-β-alanine

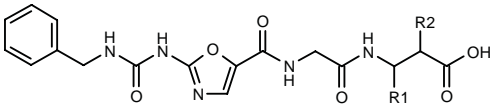


C22 H22 N6 O6; Mol wt: 466.4518

ACTION – An inhibitor of α_vβ₃ integrin (IC₅₀ = 0.00028 μM) with potential in the treatment of atherosclerosis, rheumatoid arthritis, restenosis, angioplasty, cancer, osteoporosis, thrombosis, inflammation, psoriasis and viral and parasitic infections. Other exemplified compounds include the following:



Compound	R1	Formula
296669	3-Pyr	C ₂₃ H ₂₃ N ₅ O ₅ S
296670	3,5-(Cl)2-Ph	C ₂₄ H ₂₂ Cl ₂ N ₄ O ₅ S
296671	4-Me-Ph	C ₂₅ H ₂₆ N ₄ O ₅ S



Compound	R1	R2	Formula
296672	3,5-(Cl)2-Ph	H	C ₂₃ H ₂₁ Cl ₂ N ₅ O ₆
296674	H	NHCO2CH2Ph	C ₂₅ H ₂₆ N ₆ O ₈

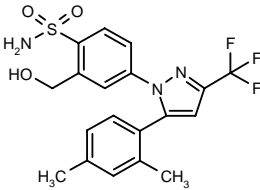
SOURCE – BASF.

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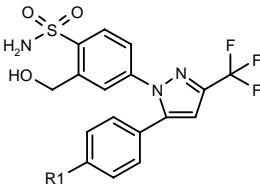
296823

4-[5-(2,4-Dimethylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-2-(hydroxymethyl)benzenesulfonamide



C19 H18 F3 N3 O3 S; Mol wt: 425.4292

ACTION – Antiinflammatory agent that selectively inhibits cyclooxygenase type 2 (COX-2). This compound is expected to be of use for the treatment of COX-2-mediated disorders such as inflammation, arthritis, pain, Alzheimer’s disease, dysmenorrhea, asthma, etc. Other exemplified pyrazoles include the following:



Compound	R1	Formula
296824	OMe	C ₁₈ H ₁₆ F ₃ N ₃ O ₄ S
296825	SMe	C ₁₈ H ₁₆ F ₃ N ₃ O ₃ S ₂
296826	N(Me)2	C ₁₉ H ₁₉ F ₃ N ₄ O ₃ S

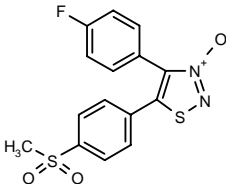
SOURCE – Dr. Reddy’s Research Foundation.

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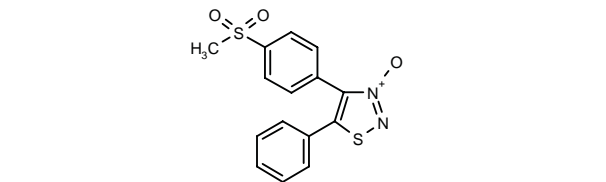
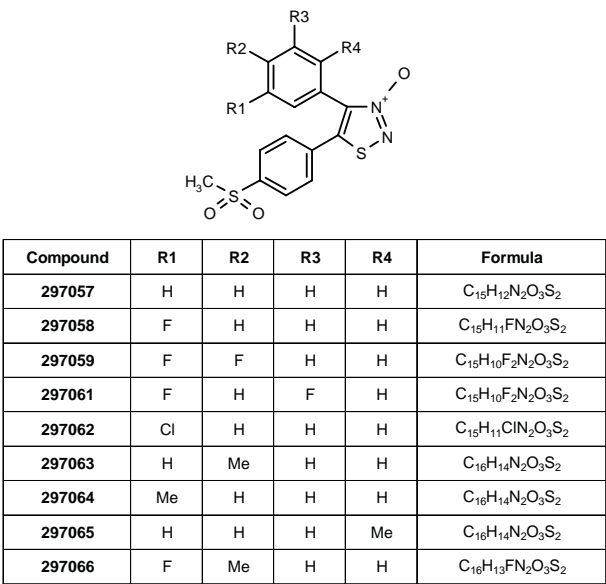
297056

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1,2,3-thiadiazole 3-oxide



C15 H11 F N2 O3 S2; Mol wt: 350.3929

ACTION – Antiinflammatory agent that selectively inhibits cyclooxygenase type 2 (COX-2; IC₅₀ = 0.6 and 18 μM for inhibition of COX-2 and COX-1, respectively). This compound was active in the rat paw edema assay with an ED₅₀ of 0.5 mg/kg p.o. Other specifically claimed diphenyl-1,2,3-thiadiazol-3-oxides are:



297060: C15 H12 N2 O3 S2

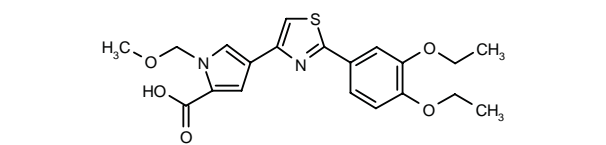
SOURCE – Merck Frosst.

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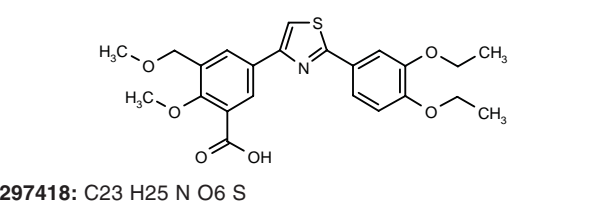
297417

4-[2-(3,4-Diethoxyphenyl)thiazol-4-yl]-1-(methoxymethyl)-pyrrole-2-carboxylic acid



C20 H22 N2 O5 S; Mol wt: 402.4688

ACTION – An inhibitor of superoxide anion radical release (IC₅₀ = 0.003 μM in human neutrophils stimulated with fMLP), also shown to inhibit the fMLP-stimulated adhesion of human neutrophils (IC₅₀ = 0.05 μM) as well as lipopoly-saccharide-stimulated TNF-α production in human whole blood (IC₅₀ = 2.5 μM). Potentially useful for the treatment of a broad range of disorders such as rheumatoid arthritis, endotoxic shock, adult respiratory distress syndrome, asthma, myocardial infarction/ischemia, inflammatory bowel disease and transplant rejection. Another compound from this series of thiazole derivatives is:



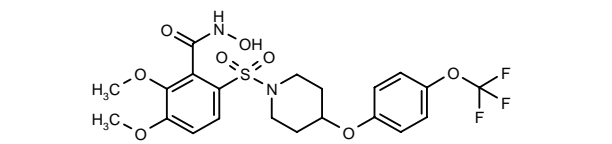
SOURCE – Otsuka.

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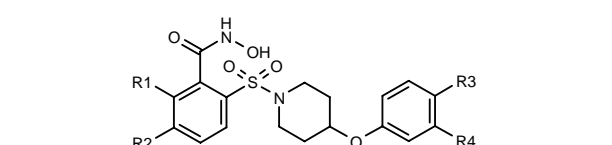
297556

2,3-Dimethoxy-6-[4-[4-(trifluoromethoxy)phenoxy]-piperidin-1-ylsulfonyl]benzohydroxamic acid



C21 H23 F3 N2 O8 S; Mol wt: 520.4787

ACTION – Matrix metalloproteinase inhibitor with excellent inhibitory activity against MMP-2 (gelatinase A; IC₅₀ = 0.9 nM), MMP-9 (gelatinase B; IC₅₀ = 1.5 nM) and MMP-13 (collagenase 3; IC₅₀ = 5.0 nM) while exhibiting little inhibition of MMP-1 (fibroblast collagenase; IC₅₀ > 10,000 nM). This compound is potentially useful for the treatment of rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulcer, tumor metastasis, angiogenesis, periodontal disease, proteinuria, Alzheimer's disease, coronary thrombosis, plaque formation and bone disease. Other exemplified hydroxamic acid derivatives are:



Compound	R1	R2	R3	R4	Formula
297557	-OCH2O-		CF3	H	C ₂₀ H ₁₉ F ₃ N ₂ O ₇ S
297558	OMe	OMe	OMe	H	C ₂₁ H ₂₆ N ₂ O ₈ S
297559	OMe	OMe	-OCH2O-	H	C ₂₁ H ₂₄ N ₂ O ₉ S
297560	OMe	OMe	OBu	H	C ₂₄ H ₃₂ N ₂ O ₈ S

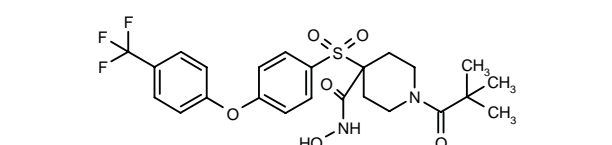
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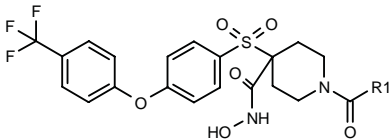
297561

1-(2,2-Dimethylpropionyl)-4-[4-[4-(trifluoromethyl)-phenoxy]phenylsulfonyl]piperidine-4-carbohydroxamic acid



C24 H27 F3 N2 O6 S; Mol wt: 528.5453

ACTION – Matrix metalloproteinase inhibitor with excellent inhibitory activity against MMP-2 (gelatinase A; IC₅₀ < 0.1 nM) and MMP-13 (collagenase 3; IC₅₀ < 0.1 nM) while exhibiting little inhibition of MMP-1 (fibroblast collagenase; IC₅₀ > 10,000 nM). This compound is potentially useful for the treatment of rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulcer, tumor metastasis, angiogenesis, periodontal disease, proteinuria, Alzheimer’s disease, coronary thrombosis, plaque formation and bone disease. Other exemplified aromatic sulfone hydroxamic acid derivatives are:



Compound	R1	Formula
297562	2-furyl	C ₂₄ H ₂₁ F ₃ N ₂ O ₇ S
297563	4-(CF ₃ O)-Ph	C ₂₇ H ₂₂ F ₆ N ₂ O ₇ S
297564	NHCH ₂ NCO	C ₂₂ H ₂₁ F ₃ N ₄ O ₇ S

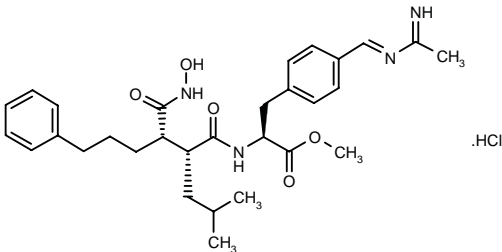
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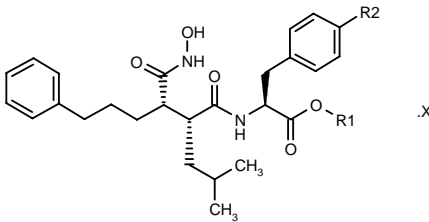
297586

4-(Acetimidoyliminomethyl)-N-[3(S)-(N-hydroxycarbamoyl)-2(R)-isobutyl-6-phenylhexanoyl]-L-phenylalanine methyl ester hydrochloride



C30 H40 N4 O5 . HCl; Mol wt: 573.1299

ACTION – Matrix metalloproteinase (MMP) inhibitor with potent activity against human fibroblast collagenase (MMP-1; IC₅₀ = 30 nM) and human stromelysin 1 (MMP-3; IC₅₀ = 20 nM), also reported to inhibit TNF-α convertase (TACE). Potentially useful for the treatment of osteoarthritis, periodontal disease, corneal ulcer, multiple sclerosis, psoriasis and allergic diseases. Other exemplified compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2	X	Formula
297587	Me	CH ₂ NH ₂	acetate	C ₂₈ H ₃₉ N ₃ O ₅ ·C ₂ H ₄ O ₂
297588	H	CH ₂ NH ₂	HCl	C ₂₇ H ₃₇ N ₃ O ₅ ·HCl
297589	H	CH=NC(=NH)Me	acetate	C ₂₉ H ₃₈ N ₄ O ₅ ·C ₂ H ₄ O ₂
297590	H	CH ₂ NH ₂		C ₂₇ H ₃₇ N ₃ O ₅

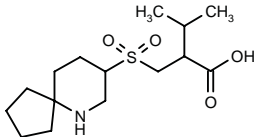
SOURCE – Fuji Yakuhin.

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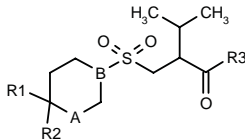
297606

2-(6-Azaspiro[4.5]dec-8-ylsulfonylmethyl)-3-methylbutyric acid



C15 H27 N O4 S; Mol wt: 317.4473

ACTION – An inhibitor of matrix metalloproteinases (MMPs), ADAM, ADAM-TS and/or TNF-α production that may also inhibit MMP-mediated membrane shedding events. Potentially useful for the treatment of osteoarthritis, rheumatoid arthritis and metastatic tumors, among other conditions. Other specifically claimed hydroxamic and carboxylic acid derivatives are:



Compound	R1,R2	R3	A	B	Formula
297607	-CH(4-Cl-Ph)-	OH	CH ₂	N	C ₁₈ H ₂₄ ClNO ₄ S
297608	-(CH ₂) ₄ -	NHOH	NH	CH	C ₁₅ H ₂₈ N ₂ O ₄ S
297609	-CH(4-Cl-Ph)-	NHOH	CH ₂	N	C ₁₈ H ₂₅ ClN ₂ O ₄ S

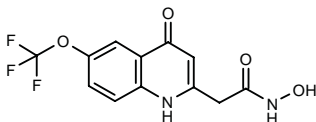
SOURCE – Darwin Discovery.

REFERENCES

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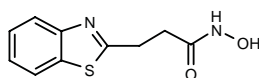
297610

2-[4-Oxo-6-(trifluoromethoxy)-1,4-dihydroquinolin-2-yl]acetohydroxamic acid



C₁₂ H₉ F₃ N₂ O₄; Mol wt: 302.2071

ACTION – An inhibitor of matrix metalloproteinases (MMPs), ADAM, ADAM-TS and/or TNF- α production that may also inhibit MMP-mediated membrane shedding events. Potentially useful for the treatment of osteoarthritis, rheumatoid arthritis and metastatic tumors, among other conditions. Another specifically claimed compound from this series of hydroxamic and carboxylic acid derivatives is:



297611: C₁₀ H₁₀ N₂ O₂ S

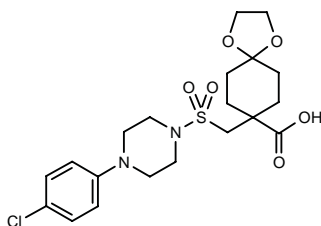
SOURCE – Darwin Discovery.

REFERENCES

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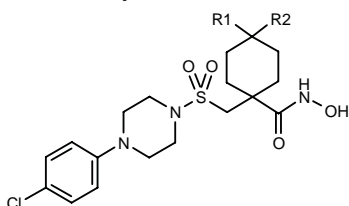
297612

8-[4-(4-Chlorophenyl)piperazin-1-ylsulfonylmethyl]-1,4-dioxaspiro[4.5]decane-8-carboxylic acid



C₂₀ H₂₇ Cl N₂ O₆ S; Mol wt: 458.9603

ACTION – An inhibitor of matrix metalloproteinases (MMPs), ADAM, ADAM-TS and/or TNF- α production that may also inhibit MMP-mediated membrane shedding events. Potentially useful for the treatment of osteoarthritis, rheumatoid arthritis and metastatic tumors, among other conditions. Other specifically claimed hydroxamic and carboxylic acid derivatives are:



Compound	R1,R2	Formula
297613	-OCH ₂ CH ₂ O-	C ₂₀ H ₂₈ ClN ₂ O ₆ S
297614	-O-	C ₁₈ H ₂₄ ClN ₂ O ₅ S
297615	-N(OMe)-	C ₁₉ H ₂₇ ClN ₄ O ₅ S

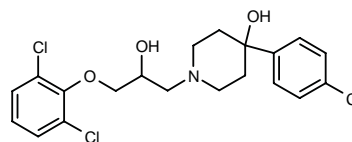
SOURCE – Darwin Discovery.

REFERENCES

1. Baxter, A.D. et al. (Darwin Discovery Ltd.) *Hydroxamic and carboxylic acid derivs.* WO 0069839.

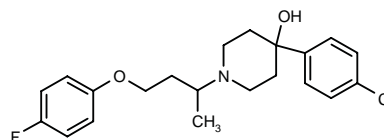
297626

4-(4-Chlorophenyl)-1-[3-(2,6-dichlorophenoxy)-2-hydroxypropyl]piperidin-4-ol



C₂₀ H₂₂ Cl₃ N O₃; Mol wt: 430.7568

ACTION – Agent for the treatment of cartilage and bone disorders including osteoarthritis, rheumatoid arthritis and other arthritic conditions, spondylosis, bone fracture, systemic lupus erythematosus and rheumatic fever that acts by promoting proteoglycan production. Another compound from this series of phenoxypropyl amine derivatives is:



297627: C₂₁ H₂₅ Cl F N O₂

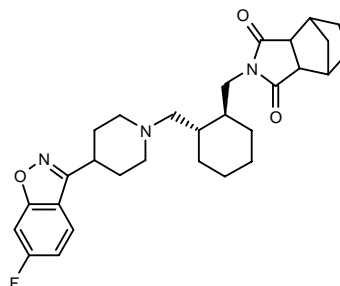
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Hashimoto, G. (Sumitomo Pharmaceuticals Co., Ltd.) *Proteoglycan production promoting agents containing phenoxy propyl amine derivs.* JP 2000281580.

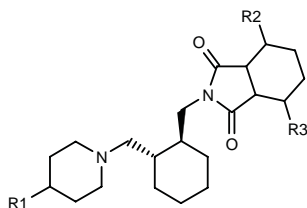
297628

2-[(1S,2S)-2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-ylmethyl]cyclohexylmethyl]perhydro-4,7-methanoisoindole-1,3-dione



C₂₉ H₃₆ F N₃ O₃; Mol wt: 493.6194

ACTION – Agent for the treatment of cartilage and bone disorders including osteoarthritis, rheumatoid arthritis and other arthritic conditions, spondylosis, bone fracture, systemic lupus erythematosus and rheumatic fever that acts by promoting proteoglycan production. Other compounds from this series of imido derivatives include the following:



Compound	R1	R2	R3	Formula
297629	4-F-PhS	H	H	C ₂₇ H ₃₈ ClFN ₂ O ₂ S
297630	5-benzofuryl	-CH2-		C ₃₀ H ₃₈ N ₂ O ₃

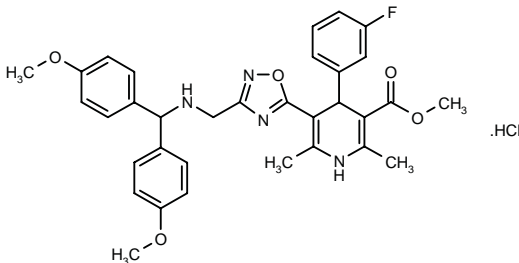
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Hashimoto, G. (Sumitomo Pharmaceuticals Co., Ltd.) *Proteoglycan production promoting agents containing imido derivs.* JP 2000281576.

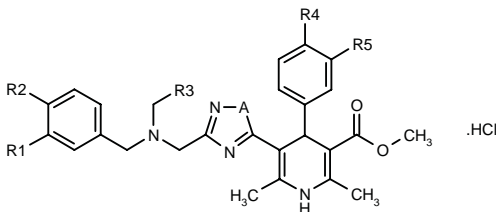
297631

5-[3-[Bis(4-methoxyphenyl)methylaminomethyl]-1,2,4-oxadiazol-5-yl]-4-(3-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylic acid methyl ester hydrochloride

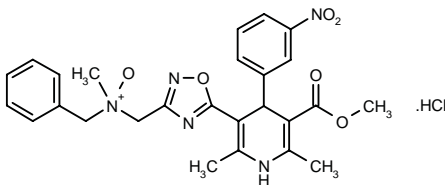


C33 H33 F N4 O5 . HCl; Mol wt: 621.1056

ACTION – Agent for the treatment of cartilage and bone disorders including osteoarthritis, rheumatoid arthritis and other arthritic conditions, spondylosis, bone fracture, systemic lupus erythematosus and rheumatic fever that acts by promoting proteoglycan production. Other compounds from this series of oxadiazolyl-1,4-dihydropyridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
297632	OMe	OMe	H	H	NO2	O	C ₂₈ H ₃₁ N ₅ O ₇ .HCl
297633	-OCH2O-		H	H	NO2	O	C ₂₇ H ₂₇ N ₅ O ₇ .HCl
297634	CF3	H	H	H	NO2	O	C ₂₇ H ₂₆ F ₃ N ₅ O ₅ .HCl
297635	H	H	Me	H	NO2	O	C ₂₇ H ₂₉ N ₅ O ₅ .HCl
297636	H	H	H	NO2	H	O	C ₂₆ H ₂₇ N ₅ O ₅ .HCl
297637	H	H	H	H	NO2	S	C ₂₆ H ₂₇ N ₅ O ₄ S.HCl



297638: C26 H27 N5 O6 . HCl

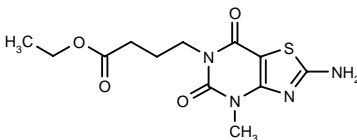
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Hashimoto, G. (Sumitomo Pharmaceuticals Co., Ltd.) *Proteoglycan production promoting agents containing oxadiazolyl-1,4-dihydropyridine derivs.* JP 2000281579.

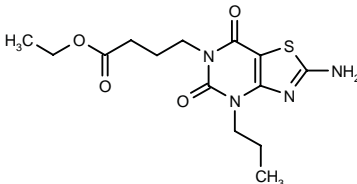
297640

4-(2-Amino-4-methyl-5,7-dioxo-4,5,6,7-tetrahydro-thiazolo[4,5-*d*]pyrimidin-6-yl)butyric acid ethyl ester



C12 H16 N4 O4 S; Mol wt: 312.3484

ACTION – Agent for the treatment of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, asthma, psoriasis and inflammatory bowel disease, as well as cardiomyopathy, congestive heart failure and insulin-resistant diabetes, with cytokine-, particularly TNF- α -, inhibitory activity. *In vitro*, compound inhibited lipopolysaccharide (LPS)-stimulated TNF- α production in human peripheral blood mononuclear cells with an IC₅₀ value of 676 nM, being more potent than rolipram (IC₅₀ = 2500 nM) and SB-210313 (IC₅₀ = 1146 nM). In addition, it was found to inhibit LPS-stimulated IL-1 β production in human mono-cytes with an IC₅₀ value of about 1-3 μ M. Compound inhibited human phosphodiesterase type 4 (PDE4) with an IC₅₀ value of only 43 μ M, compared to 196 nM for rolipram, which shows that it does not act via inhibition of PDE4. When tested *in vivo*, it was shown to dose-dependently (25-100 mg/kg p.o.) inhibit LPS-stimulated TNF- α production in mice, with a good duration of action (> 24 h at the dose of 100 mg/kg p.o.). In addition, it was effective in an adjuvant-induced arthritis model in rats, giving about 50% inhibition at 100 mg/kg/day p.o. x 30 days. Another exemplified compound from this series of thiazolo[4,5-*d*]pyrimidine derivatives is:



297641: C14 H20 N4 O4 S

SOURCE – University of California, Oakland, Oakland, CA (US).

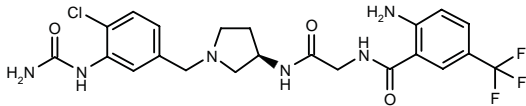
REFERENCES

1. Carson, D.A. et al. (University of California, Oakland) *Thiazolopyrimidines useful as TNF α inhibitors.* WO 0069861.

297642

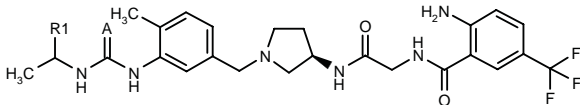
2-Amino-*N*-[2-[1-(4-chloro-3-ureidobenzyl)pyrrolidin-3(*R*)-ylamino]-2-oxoethyl]-5-(trifluoromethyl)benzamide

*N*²-[2-Amino-5-(trifluoromethyl)benzoyl]-*N*¹-[1-(4-chloro-3-ureidobenzyl)pyrrolidin-3(*R*)-yl]glycinamide



C22 H24 Cl F3 N6 O3; Mol wt: 512.9176

ACTION – Agent for the treatment of rheumatoid arthritis, atherosclerosis, psoriasis, asthma, ulcerative colitis, nephritis and other disorders characterized by tissue infiltration of monocytes and lymphocytes, a chemokine receptor antagonist that inhibits the action of chemokines such as macrophage inflammatory protein-1 α (MIP-1 α) and monocyte chemotactic protein-1 (MCP-1) on target cells. *In vitro*, compound was shown to inhibit the binding of human MCP-1 to human monocytic leukemia THP-1 cells, producing > 80% inhibition at 1 μ M, as well as MCP-1-induced chemotaxis of THP-1 cells, with an IC₅₀ value < 0.1 μ M. Other exemplified compounds within this series of ureido-substituted cyclic amine derivatives include the following:



Compound	R1	A	Formula
297643	Me	O	C ₂₆ H ₃₃ F ₃ N ₆ O ₃
297644	H	S	C ₂₅ H ₃₁ F ₃ N ₆ O ₂ S

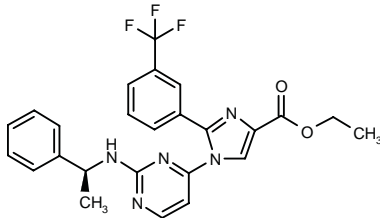
SOURCES – DuPont Pharmaceuticals; Teijin.

REFERENCES

1. Shiota, T. et al. (Teijin Ltd.;DuPont Pharmaceuticals Research Labs.) *Ureido-substd. cyclic amine derivs. and their use as drug.* WO 0069815.

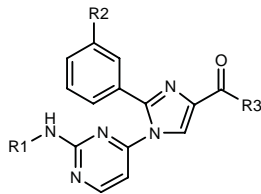
297645

1-[2-[1(*S*)-Phenylethylamino]pyrimidin-4-yl]-2-[3-(trifluoromethyl)phenyl]-1*H*-imidazole-4-carboxylic acid ethyl ester



C25 H22 F3 N5 O2; Mol wt: 481.4758

ACTION – An inhibitor of the production or activity of cytokines such as IL-1, IL-6, IL-8 and TNF- α with potential for the treatment of disorders where cytokines are involved such as rheumatoid arthritis, osteoarthritis, sepsis, inflammatory bowel disease, atherosclerosis, cachexia, gout, bone resorption disorders, transplant rejection, fever and AIDS-related complex. Other specifically claimed compounds from this series of substituted imidazole derivatives include the following:



Compound	R1	R2	R3	Formula
297646	(S)-CH(Me)Ph	CF3	OH	C ₂₃ H ₁₈ F ₃ N ₅ O ₂
297647	(S)-CH(Me)Ph	CF3	1-(t-BuOCO)-4-Pip-NH	C ₃₃ H ₃₆ F ₃ N ₇ O ₃
297648	(S)-CH(Me)Ph	CF3	4-Pip-NH	C ₂₈ H ₂₈ F ₃ N ₇ O
297649	(S)-CH(Me)Ph	CF3	1-Piz	C ₂₇ H ₂₆ F ₃ N ₇ O
297650	(S)-CH(Me)Ph	CF3	NHCH2CH2N(Me)2	C ₂₇ H ₂₈ F ₃ N ₇ O
297651	(S)-CH(Me)Ph	CF3	3(S)-quinuclidinyl-NH	C ₃₀ H ₃₀ F ₃ N ₇ O
297652	(S)-CH(Me)Ph	CF3	1-Pip	C ₂₈ H ₂₇ F ₃ N ₆ O
297653	(S)-CH(Me)Ph	H	OEt	C ₂₄ H ₂₃ N ₅ O ₂
297654	(S)-CH(Me)Ph	H	OH	C ₂₂ H ₁₉ N ₅ O ₂
297655	(S)-CH(Me)Ph	H	1-Pip	C ₂₇ H ₂₈ N ₆ O
297656	(S)-CH(Me)Ph	H	NHCH2CH2N(Me)2	C ₂₆ H ₂₈ N ₇ O
297657	(S)-CH(Me)Ph	H	4-(t-BuOCO)-1-Piz	C ₃₁ H ₃₆ N ₇ O ₃
297658	(S)-CH(Me)Ph	H	1-Piz	C ₂₈ H ₂₇ N ₇ O
297659	cyclobutyl	CF3	OEt	C ₂₁ H ₂₀ F ₃ N ₅ O ₂
297660	t-Bu	CF3	OEt	C ₂₁ H ₂₂ F ₃ N ₅ O ₂
297661	2-Cl-PhCH2CH2	CF3	OEt	C ₂₅ H ₂₁ ClF ₃ N ₅ O ₂
297662	2-F-PhCH2	CF3	OEt	C ₂₄ H ₁₉ F ₄ N ₅ O ₂

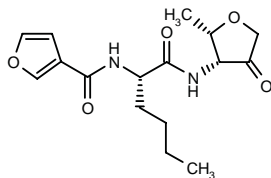
SOURCE – Merck & Co.

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1. Liverton, N.J. et al. (Merck & Co., Inc.) *Cpds. having cytokine inhibitory activity.* WO 0069848.

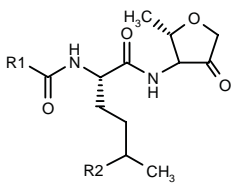
297675

*N*²-(3-Furanylcarbonyl)-*L*-norleucine 2(*S*)-methyl-4-oxo-tetrahydrofuran-3(*R*)-yl amide



C16 H22 N2 O5; Mol wt: 322.3588

ACTION – Selective cathepsin S inhibitor that exhibited a K_i of 1.0 μ M for inhibition of mammalian cathepsin S versus a K_i > 100 μ M for mammalian cathepsins L and K. Potentially useful for the treatment of autoimmune diseases, rheumatoid arthritis, allergy, multiple sclerosis and other cathepsin S-related conditions. Other exemplified furanone derivatives include the following:



Compound	R1	R2	Isomer	Formula
297685	3-furyl	H	S	C ₁₆ H ₂₂ N ₂ O ₅
297687	3-furyl	Me	R	C ₁₇ H ₂₄ N ₂ O ₅
297689	3-furyl	Me	S	C ₁₇ H ₂₄ N ₂ O ₅
297691	4-morpholinyl	Me	R	C ₁₇ H ₂₈ N ₃ O ₅
297694	4-morpholinyl	Me	S	C ₁₇ H ₂₈ N ₃ O ₅

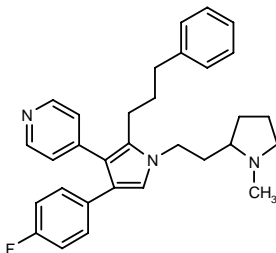
SOURCES – Genzyme General; Medivir.

REFERENCES

1. Quibell, M. and Taylor, S. (Genzyme Corp.) *Furanone derivs. as inhibitors of cathepsin S*. WO 0069855.

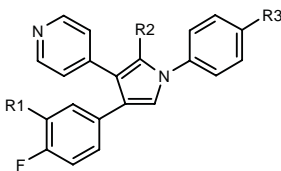
297793

4-[4-(4-Fluorophenyl)-1-[2-(1-methylpyrrolidin-2-yl)ethyl]-2-(3-phenylpropyl)-1*H*-pyrrol-3-yl]pyridine



C31 H34 F N3; Mol wt: 467.6286

ACTION – An inhibitor of the production of TNF- α and/or p38 activity, as demonstrated by inhibition of lipopoly-saccharide-stimulated TNF- α production both *in vitro* in human peripheral blood mononuclear cells (IC₅₀ = 5 nM) and *in vivo* in mice (100% inhibition at 10 mg/kg p.o.). Potentially useful for the treatment of inflammatory disorders, particularly rheumatoid arthritis, but also osteoporosis, osteoarthritis, allergic inflammation, periodontal disorder, inflammatory bowel disease, septic shock, diabetes, cachexia, pulmonary fibrosis, myas-thenia gravis, hepatitis, primary biliary cirrhosis, acute pancreatitis, allograft rejection, psoriasis, ischemia, restenosis, atherosclerosis, HIV infection, multiple sclero-sis and Alzheimer’s disease. Other specifically claimed compounds from this series of substituted 3-pyridyl-4-arylpyrroles are:



Compound	R1	R2	R3	Formula
297794	F	H	CN	C ₂₂ H ₁₃ F ₂ N ₃
297795	H	(CH ₂) ₃ Ph	NO ₂	C ₃₀ H ₂₄ FN ₃ O ₂
297796	H	(CH ₂) ₃ Ph	NHAc	C ₃₂ H ₂₈ FN ₃ O
297797	H	(CH ₂) ₃ Ph	NH ₂	C ₃₀ H ₂₆ FN ₃

SOURCE – Ortho-McNeil.

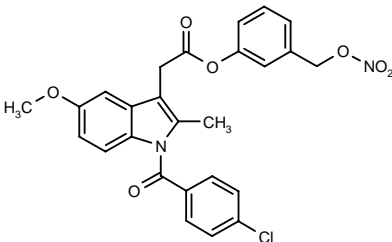
REFERENCES

1. Bullington, J. (Ortho-McNeil Pharmaceutical, Inc.) *Substd. 3-pyridyl-4-arylpyrroles, and related therapeutic and prophylactic methods*. WO 0069847.

NCX-530

290500

2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid 3-(nitrooxymethyl)phenyl ester



C26 H21 Cl N2 O7; Mol wt: 508.9119

ACTION – Nitric oxide (NO)-releasing derivative of indomethacin that retains the antiinflammatory activity of the parent compound but does not possess ulcerogenic activity. Compound induced dose-dependent gastric cytoprotection against HCl/ethanol injury and promoted healing of gastric ulcers induced in mice by thermal cauterization, whereas indomethacin delayed healing of ulcers. Compound given as a single dose of 14.2 mg/kg s.c. did not induce significant intestinal damage or significant changes in inducible nitric oxide synthase and myeloperoxidase activities; it enhanced small intestinal mucus and fluid secretion and, unlike indomethacin, did not increase enterobacteria translocation in the intestinal mucosa. On the other hand, NCX-530 was as effective as indomethacin in inhibiting cyclooxygenase and exerting antiinflammatory effects in the carrageenan-induced rat paw edema model.

SOURCES – Kyoto Pharmaceutical University, Kyoto (JP); NicOx.

REFERENCES

1. Del Soldato, P. and Garufi, M. (NicOx SA) *Synthesis method of nitroxymethylphenyl esters of aspirin derivs*. WO 0044705.

2. Del Soldato, P. and Sannicolo', F. (NicOx SA) *Nitric ester derivs. and their use in urinary incontinence and other diseases*. JP 2000517332, WO 9809948.

3. Mizoguchi, H. et al. *Lack of small intestinal ulcerogenecity of nitric oxide-releasing indomethacin, NCX-530, in rats*. Aliment Pharmacol Ther 2001, 15(2): 257.

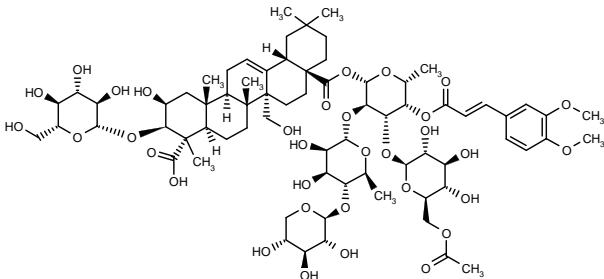
4. Ogawa, Y. et al. *Lack of small intestinal ulcerogenicity of nitric oxide-releasing indomethacin (NCX-530) in rats*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-182.

5. Takeuchi, K. et al. *Effects of nitric oxide-releasing indomethacin, NCX-530, on gastric ulcerogenic and healing responses*. 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 32.

SECURIOSIDE A

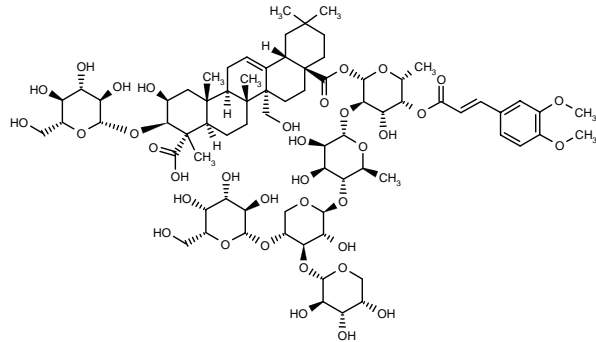
299793

(2β,3β,4β)-3-(β-D-Glucopyranosyloxy)-2,27-dihydroxyolean-12-ene-23,28-dioic acid 28-[3-O-(6-O-acetyl-β-D-glucopyranosyl)-2-O-[4-O-(β-D-xylopyranosyloxy)-6-deoxy-α-L-mannopyranosyl]-4-O-[3-(3,4-dimethoxyphenyl)-2(E)-propenoyl]-6-deoxy-β-D-galactopyranosyl] ester



C72 H106 O33; Mol wt: 1499.5960

ACTION – Potential antiinflammatory agent, a triterpene bisdesmoside isolated from the roots of *Securidaca inappendiculata*, with potent and selective cytotoxic activity against macrophage colony-stimulating factor (M-CSF)-stimulated murine macrophages (IC₅₀ < 0.25 μM). Compound was not active against nonstimulated macrophages, granulocyte–macrophage colony-stimulating factor (GM-CSF)-stimulated macrophages, bone marrow cells or lymphocytes, and appeared to act by inducing apoptosis. *In vivo* evaluation of compound in models of rheumatoid arthritis and atherosclerosis is in progress. Another compound isolated from this source is:



Securioside B [299796]: C75 H112 O36

SOURCES – Kaneka; Teikyo University, Utsunomiya (JP); Tokyo University of Pharmacy and Life Science, Tokyo (JP).

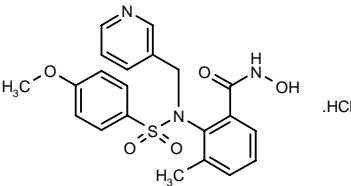
REFERENCES

1. Kuroda, M. et al. *Securiosides A and B, novel acylated triterpene bisdesmosides with selective cytotoxic activity against M-CSF-stimulated macrophages.* Bioorg Med Chem Lett 2001, 11(3): 371.

WAY-151693

299237

2-[N-(4-Methoxyphenylsulfonyl)-N-(3-pyridinylmethyl)-amino]-3-methylbenzohydroxamic acid hydrochloride



C21 H21 N3 O5 S.HCl; Mol wt: 463.9398

ACTION – Matrix metalloproteinase (MMP) inhibitor active against gelatinase B (MMP-9; IC₅₀ = 5 nM) and collagenase 3 (MMP-13; IC₅₀ = 8 nM), with potency comparable to CGS-27023A (IC₅₀ = 9 and 8 nM, respectively) and approximately 30-fold selectivity over interstitial collagenase (MMP-1). In the bovine articular cartilage explant assay, both compound and CGS-27023A produced inhibition of collagen degradation (49% at 1 μM). Moreover, compound exhibited *in vivo* activity in a murine model, where it was found to inhibit gelatinase B activity with an ED₅₀ of 33 mg/kg p.o., and in a rat sponge-wrapped cartilage model, where it gave 51% inhibition of collagen degradation at the dose of 50 mg/kg/day i.p. Potentially useful for the treatment of osteoarthritis or tumor metastasis.

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Levin, J.I. et al. (American Cyanamid Co.) *The preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors.* WO 9816503.

2. Levin, J.I. et al. (American Cyanamid Co.) *Preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase inhibitors.* US 5929097.

3. Levin, J.I. et al. *The discovery of anthranilic acid-based MMP inhibitors. Part 1. SAR of the 3-position.* Bioorg Med Chem Lett 2001, 11(2): 235.

4. Moy, F.J. et al. *¹H, ¹⁵N, ¹³C and ¹³CO assignments and secondary structure determination of collagenase-3 (MMP-13) complexed with a hydroxamic acid inhibitor.* J Biomol NMR 2000, 17(3): 269.

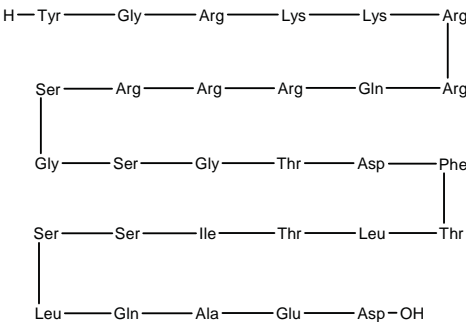
5. Moy, F.J. et al. *High-resolution solution structure of the catalytic fragment of human collagenase-3 (MMP-13) complexed with a hydroxamic acid inhibitor.* J Mol Biol 2000, 302(3): 671.

TREATMENT OF OTHER
AUTOIMMUNE DISORDERS

TAT-TISS PEPTIDE

300052

L-Tyrosyl-glycyl-L-arginyl-L-lysyl-L-lysyl-L-arginyl-L-arginyl-L-glutaminyl-L-arginyl-L-arginyl-L-arginyl-L-seryl-glycyl-L-seryl-glycyl-L-threonyl-L-aspartyl-L-phenylalanyl-L-threonyl-L-leucyl-L-threonyl-L-isoleucyl-L-seryl-L-seryl-L-leucyl-L-glutaminyl-L-alanyl-L-glutamyl-L-aspartic acid



C140 H237 N51 O46; Mol wt: 3370.7230

ACTION – Hsp70-binding fusion peptide consisting of the HIV TAT sequence and the V_L-derived sequence of the amyloidogenic SMA protein, proven to significantly reduce the amount of insoluble SMA and the formation of aggresomes. Potential therapeutic approach to the treatment of amyloidosis, particularly light chain-related amyloidosis.

SOURCES – Argonne National Laboratory, Argonne, IL (US); University of Chicago, Chicago, IL (US).

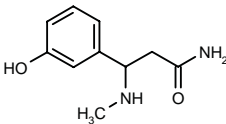
REFERENCES

1. Dul, J.L. et al. *Hsp70 and antifibrillogenic peptides promote degradation and inhibit intracellular aggregation of amyloidogenic light chains.* J Cell Biol 2001, 152(4): 705.

IMMUNOMODULATING AGENTS

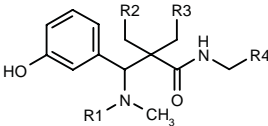
297280

3-(3-Hydroxyphenyl)-3-(methylamino)propionamide



C10 H14 N2 O2; Mol wt: 194.2326

ACTION – Potent and selective mu opioid receptor ligand with potential in the treatment of a broad range of disorders including inflammatory diseases such as arthritis and psoriasis, respiratory diseases such as asthma, gastrointestinal diseases such as irritable bowel syndrome and gastritis, stroke, shock, urogenital tract disorders such as urinary incontinence, alcohol, tobacco and drug addiction, pain and transplant rejection. Other exemplified compounds from this series of 3-(3-hydroxyphenyl)-3-aminopropionamide derivatives are:



Compound	R1	R2	R3	R4	Formula
297283	H	-(CH2)3-		Ph	C ₂₂ H ₂₈ N ₂ O ₂
297284	H	-(CH2)3-		1-Naph	C ₂₆ H ₃₀ N ₂ O ₂
297285	H	-(CH2)3-		CH2CH2Ph	C ₂₄ H ₃₂ N ₂ O ₂
297286	H	-(CH2)3-		CH2Ph	C ₂₃ H ₃₀ N ₂ O ₂
297287	H	H	H	CH2Ph	C ₂₀ H ₂₆ N ₂ O ₂
297288	H	H	H	1-Naph	C ₂₃ H ₂₈ N ₂ O ₂
297289	H	H	H	CH2CH2Ph	C ₂₁ H ₂₈ N ₂ O ₂
297298	H	H	H	cyclopropyl	C ₁₆ H ₂₄ N ₂ O ₂
297299	H	H	H	cyclohexyl	C ₁₉ H ₃₀ N ₂ O ₂
297300	H	H	H	Ph	C ₁₉ H ₂₄ N ₂ O ₂
297301	cyclopropyl-CH2	H	H	CH2Ph	C ₂₄ H ₃₂ N ₂ O ₂
297302	2-thiazolyl-CH2	H	H	CH2Ph	C ₂₄ H ₂₉ N ₃ O ₂ S
297303	Pr	H	H	CH2Ph	C ₂₃ H ₃₂ N ₂ O ₂
297306	i-Bu	H	H	CH2Ph	C ₂₄ H ₃₄ N ₂ O ₂

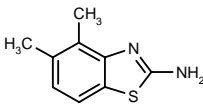
SOURCE – Pfizer.

REFERENCES

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297542

4,5-Dimethylbenzothiazol-2-amine



C9 H10 N2 S; Mol wt: 178.2580

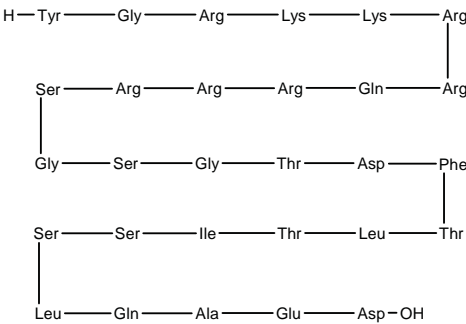
ACTION – Potassium channel modulator, particularly active at calcium-activated SK_{Ca}, IK_{Ca} and BK_{Ca} channels, that inhibits Ca²⁺-activated K⁺ channels in T- and B-lymphocytes and produced a concentration-dependent decrease in T-cells in an antigen-induced T-cell proliferation assay. Potentially useful for the treatment of diseases or conditions associated with these channels and preferably those related with immune dysfunction. Other specifically claimed compounds from this series are:

TREATMENT OF OTHER
AUTOIMMUNE DISORDERS

TAT-TISS PEPTIDE

300052

L-Tyrosyl-glycyl-L-arginyl-L-lysyl-L-lysyl-L-arginyl-L-arginyl-L-glutaminyl-L-arginyl-L-arginyl-L-arginyl-L-seryl-glycyl-L-seryl-glycyl-L-threonyl-L-aspartyl-L-phenylalanyl-L-threonyl-L-leucyl-L-threonyl-L-isoleucyl-L-seryl-L-seryl-L-leucyl-L-glutaminyl-L-alanyl-L-glutamyl-L-aspartic acid



C140 H237 N51 O46; Mol wt: 3370.7230

ACTION – Hsp70-binding fusion peptide consisting of the HIV TAT sequence and the V_L-derived sequence of the amyloidogenic SMA protein, proven to significantly reduce the amount of insoluble SMA and the formation of aggresomes. Potential therapeutic approach to the treatment of amyloidosis, particularly light chain-related amyloidosis.

SOURCES – Argonne National Laboratory, Argonne, IL (US); University of Chicago, Chicago, IL (US).

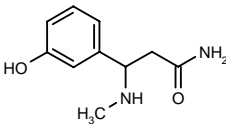
REFERENCES

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IMMUNOMODULATING AGENTS

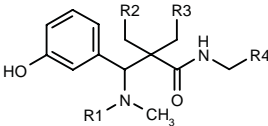
297280

3-(3-Hydroxyphenyl)-3-(methylamino)propionamide



C10 H14 N2 O2; Mol wt: 194.2326

ACTION – Potent and selective mu opioid receptor ligand with potential in the treatment of a broad range of disorders including inflammatory diseases such as arthritis and psoriasis, respiratory diseases such as asthma, gastrointestinal diseases such as irritable bowel syndrome and gastritis, stroke, shock, urogenital tract disorders such as urinary incontinence, alcohol, tobacco and drug addiction, pain and transplant rejection. Other exemplified compounds from this series of 3-(3-hydroxyphenyl)-3-aminopropionamide derivatives are:



Compound	R1	R2	R3	R4	Formula
297283	H	-(CH2)3-		Ph	C ₂₂ H ₂₈ N ₂ O ₂
297284	H	-(CH2)3-		1-Naph	C ₂₆ H ₃₀ N ₂ O ₂
297285	H	-(CH2)3-		CH2CH2Ph	C ₂₄ H ₃₂ N ₂ O ₂
297286	H	-(CH2)3-		CH2Ph	C ₂₃ H ₃₀ N ₂ O ₂
297287	H	H	H	CH2Ph	C ₂₀ H ₂₆ N ₂ O ₂
297288	H	H	H	1-Naph	C ₂₃ H ₂₈ N ₂ O ₂
297289	H	H	H	CH2CH2Ph	C ₂₁ H ₂₈ N ₂ O ₂
297298	H	H	H	cyclopropyl	C ₁₆ H ₂₄ N ₂ O ₂
297299	H	H	H	cyclohexyl	C ₁₉ H ₃₀ N ₂ O ₂
297300	H	H	H	Ph	C ₁₉ H ₂₄ N ₂ O ₂
297301	cyclopropyl-CH2	H	H	CH2Ph	C ₂₄ H ₃₂ N ₂ O ₂
297302	2-thiazolyl-CH2	H	H	CH2Ph	C ₂₄ H ₂₉ N ₃ O ₂ S
297303	Pr	H	H	CH2Ph	C ₂₃ H ₃₂ N ₂ O ₂
297306	i-Bu	H	H	CH2Ph	C ₂₄ H ₃₄ N ₂ O ₂

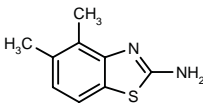
SOURCE – Pfizer.

REFERENCES

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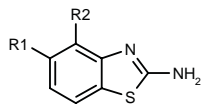
297542

4,5-Dimethylbenzothiazol-2-amine



C9 H10 N2 S; Mol wt: 178.2580

ACTION – Potassium channel modulator, particularly active at calcium-activated SK_{Ca}, IK_{Ca} and BK_{Ca} channels, that inhibits Ca²⁺-activated K⁺ channels in T- and B-lymphocytes and produced a concentration-dependent decrease in T-cells in an antigen-induced T-cell proliferation assay. Potentially useful for the treatment of diseases or conditions associated with these channels and preferably those related with immune dysfunction. Other specifically claimed compounds from this series are:



Compound	R1	R2	Formula
297543	Cl	Cl	C ₇ H ₄ Cl ₂ N ₂ S
297544	-(CH2)4-		C ₁₁ H ₁₂ N ₂ S

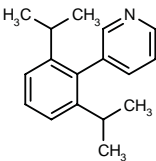
SOURCE – NeuroSearch.

REFERENCES

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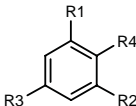
297545

3-(2,6-Diisopropylphenyl)pyridine



C17 H21 N; Mol wt: 239.3599

ACTION – Potassium channel modulator, particularly active at calcium-activated SK_{Ca}, IK_{Ca} and BK_{Ca} channels, found to increase IK current through human IK channels expressed in HEK293 cells. Potentially useful for the treatment of diseases or conditions associated with these channels and preferably those related with immune dysfunction. Other specifically claimed compounds from this series are:



Compound	R1=R2	R3	R4	Formula
297546	i-Pr	H	2-Pyr-CH2NH	C ₁₈ H ₂₄ N ₂
297547	t-Bu	Me	2-Pyr-CH2O	C ₂₁ H ₂₉ NO
297548	i-Pr	H	4-Pyr-CH=N	C ₁₈ H ₂₂ N ₂
297549	i-Pr	H	I	C ₁₂ H ₁₇ I
297550	Me	H	1-imidazolyl	C ₁₁ H ₁₂ N ₂
297551	i-Pr	NO2	NHAc	C ₁₄ H ₂₀ N ₂ O ₃
297552	Ph	NO2	OH	C ₁₈ H ₁₃ NO ₃
297553	Ph	Cl	2,5-(Me)2-1-pyrrolyl	C ₂₄ H ₂₀ ClN
297554	i-Pr	NO2	2,5-(Me)2-1-pyrrolyl	C ₁₈ H ₂₄ N ₂ O ₂
297555	Br	Cl	2,5-(Me)2-1-pyrrolyl	C ₁₂ H ₁₀ Br ₂ ClN

SOURCE – NeuroSearch.

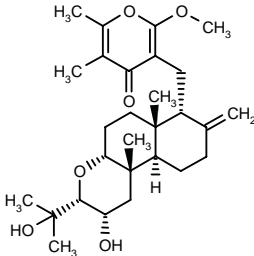
REFERENCES

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CANDELALIDE B

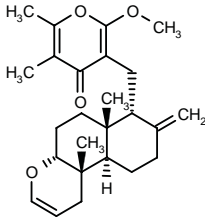
299152

3-[(2*S*,3*R*,4*aR*,6*aR*,7*R*,10*aR*,10*bS*)-2-Hydroxy-3-(1-hydroxy-1-methylethyl)-6*a*,10*b*-dimethyl-8-methylene-2,3,4*a*,5,6,6*a*,7,8,9,10,10*a*,10*b*-dodecahydro-1*H*-naphtho[2,1-*b*]pyran-7-ylmethyl]-5,6-dimethyl-2-methoxy-4*H*-pyran-4-one

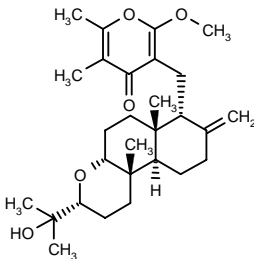


C28 H42 O6; Mol wt: 474.6338

ACTION – Potential immunosuppressant, a diterpenoid isolated from the fermentation broth of *Sesquicillium candelabrum* and proven to block voltage-gated potassium Kv1.3 channels, with an IC₅₀ of 3.7 μM in CHO cells expressing Kv1.3 channels. Other related diterpenoid pyrones are:



Candecalide A [299151]: C25 H34 O4



Candecalide C [299153]: C28 H42 O5

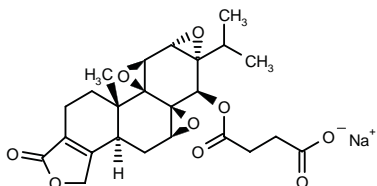
SOURCE – Merck & Co.

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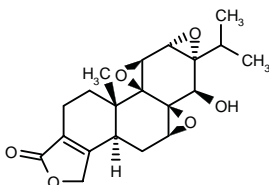
PG-490-88^{1,2,6,7,13,15,30,47,48}**290186**

4-[(3b*S*, 4a*S*, 5a*R*, 6*R*, 6a*S*, 7a*S*, 7b*S*, 8a*S*, 8b*S*)-6a-Isopropyl-8b-methyl-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahydrotrisoxireno[6,7:8a,9:4b,5]phenanthro-[1,2-*c*]furan-6-yloxy]-4-oxobutyric acid sodium salt

YM-274

C24 H27 Na O9; Mol wt: 482.4583

ACTION – Water-soluble prodrug of **triptolide**, an antiproliferative and immunosuppressive compound extracted from a Chinese herb and used in traditional Chinese medicine to treat rheumatoid arthritis. In a model of intratracheal bleomycin-induced lung fibrosis in mice, compound at a dose of 0.25 mg/kg/day i.p. for 14 days decreased inflammation and inhibited fibrosis, and appeared to act by inhibiting the proliferation and migration of myofibroblasts or by inducing myofibroblast apoptosis. In a model of lethal graft-versus-host disease (GVHD) in mice, a dose of 0.535 mg/kg/day i.p. for 3 weeks after bone marrow transplantation protected all treated recipients from GVHD for up to 100 days after transplantation, in contrast to control animals which died during this period. The prodrug inhibited alloreactive CD4+ and CD8+ T-cell expansion in the spleen, as well as IL-2-production by CD4+ cells, with no effect on CD25 expression. In addition, it induced a decrease in interferon gamma- and TNF- α -producing cells.



**Triptolide [090968]^{3-5,8-12,14,16-29,31-42}; C20 H24 O6
PG-490**

SOURCES – Duke University, Durham, NC (US); Pharmagenesis; Stanford University, Stanford, CA (US).

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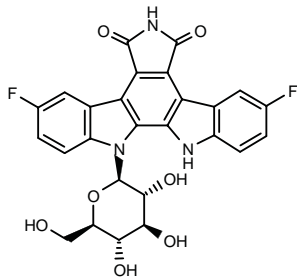
ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

FLUOROINDOLOCARBAZOLE C

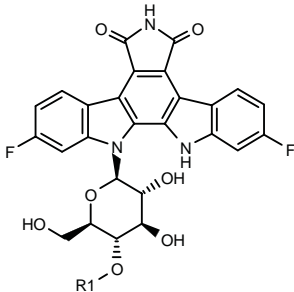
299158

3,9-Difluoro-12-(β-D-glucopyranosyl)-6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-dione



C26 H19 F2 N3 O7; Mol wt: 523.4461

ACTION – Antineoplastic agent isolated from cultures of *Saccharothrix aerocolonigenes* ATCC 39243. Compound was more potent than rebeccamycin (an indolocarbazole antitumor antibiotic extracted from the same micro-organism) in mice bearing leukemia P388, where at doses ranging from 10 to 90 mg/kg i.p. it induced a dose-dependent increase in life span (145-165%). The same effect was obtained with doses of rebeccamycin 5-10-fold higher. Other related compounds are:



Compound	R1	Formula
Fluoroindolocarbazole A [299308]	Me	C ₂₇ H ₂₁ F ₂ N ₃ O ₇
Fluoroindolocarbazole B [299310]	H	C ₂₆ H ₁₉ F ₂ N ₃ O ₇

SOURCE – Bristol-Myers Squibb.

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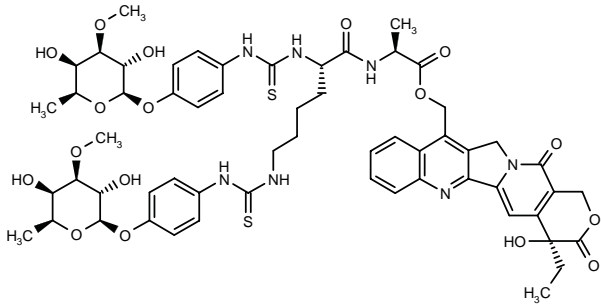
2. Saulnier, M.G. et al. (Bristol-Myers Squibb Co.) *Cytotoxic amino sugar and related sugar derivs. of indolopyrrolocarbazoles*. EP 0971717, JP 2000516250, WO 9807433.

3. Lam, K.S. et al. *Production, isolation and structure determination of novel fluoroindolocarbazoles from Saccharothrix aerocolonigenes ATCC 39243*. J Antibiot 2001, 54(1): 1.

DNA-INTERCALATING DRUGS

297231

*N*²,*N*⁶-Bis[*N*-[4-(6-deoxy-3-*O*-methyl-β-L-galactopyranosyloxy)phenyl]thiocarbamoyl]-L-lysyl-L-alanine [4(*S*)-ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinolin-11-yl)methyl ester



C58 H69 N7 O17 S2; Mol wt: 1200.3470

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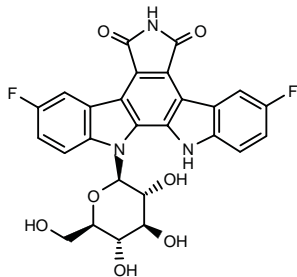
ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

FLUOROINDOLOCARBAZOLE C

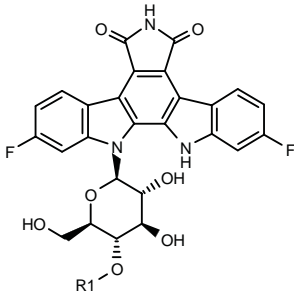
299158

3,9-Difluoro-12-(β-D-glucopyranosyl)-6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-dione



C26 H19 F2 N3 O7; Mol wt: 523.4461

ACTION – Antineoplastic agent isolated from cultures of *Saccharothrix aerocolonigenes* ATCC 39243. Compound was more potent than rebeccamycin (an indolocarbazole antitumor antibiotic extracted from the same micro-organism) in mice bearing leukemia P388, where at doses ranging from 10 to 90 mg/kg i.p. it induced a dose-dependent increase in life span (145-165%). The same effect was obtained with doses of rebeccamycin 5-10-fold higher. Other related compounds are:



Compound	R1	Formula
Fluoroindolocarbazole A [299308]	Me	C ₂₇ H ₂₁ F ₂ N ₃ O ₇
Fluoroindolocarbazole B [299310]	H	C ₂₆ H ₁₉ F ₂ N ₃ O ₇

SOURCE – Bristol-Myers Squibb.

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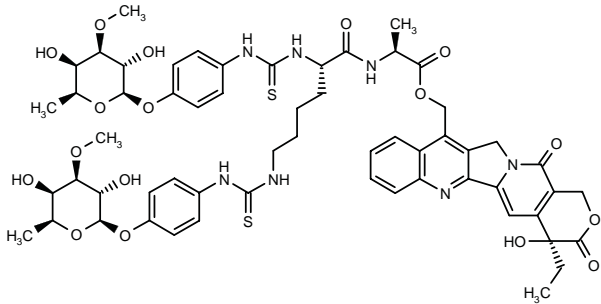
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DNA-INTERCALATING DRUGS

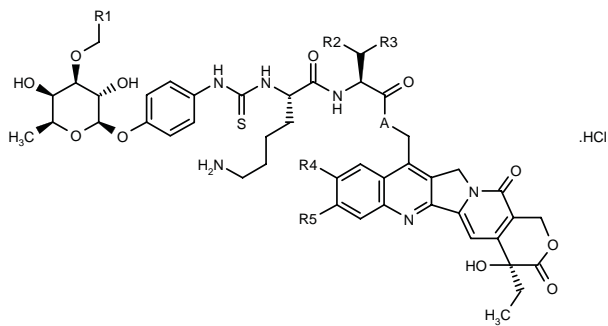
297231

*N*²,*N*⁶-Bis[*N*-[4-(6-deoxy-3-*O*-methyl-β-L-galactopyranosyloxy)phenyl]thiocarbamoyl]-L-lysyl-L-alanine [4(*S*)-ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinolin-11-yl)methyl ester

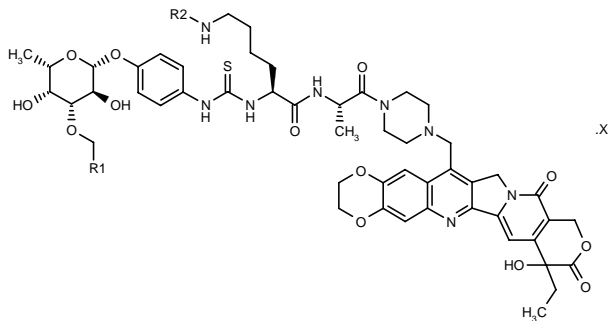


C58 H69 N7 O17 S2; Mol wt: 1200.3470

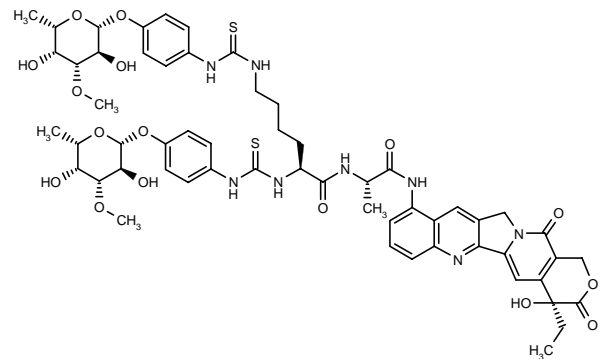
ACTION – Antineoplastic agent with high *in vitro* and *in vivo* antitumor activity, particularly against lung and colon tumors, combined with higher tolerability and tumor selectivity and improved water solubility compared to previously described camptothecin derivatives. *In vitro*, compound exhibited potent cytotoxicity against human colon SW480 and HT-29 and murine melanoma B16F10 cell lines, with respective IC₅₀ values of 0.015, 0.025 and 0.18 nM. When tested *in vivo* at 3.125-12.5 mg/kg/day i.p. x 3 days in nude mice bearing s.c.-implanted human non-small lung carcinoma LXFL-529 xenografts, a complete remission of tumors was observed at day 14 post-implantation. Other compounds from this series of glycoconjugates of camptothecin derivatives include the following:



Compound	R1	R2=R3	R4	R5	A	Formula
297232	CO2H	Me	H	H	O	C ₄₇ H ₅₆ N ₆ O ₁₄ S.HCl
297233	H	Me	H	H	O	C ₄₆ H ₅₆ N ₆ O ₁₂ S.HCl
297239	H	H	-OCH2CH2O-		NH	C ₄₆ H ₅₅ N ₇ O ₁₃ S.HCl



Compound	R1	R2	X	Formula
297235	H	4-(6-deoxy-3-O-Me-β-L-galactopyranosyloxy)-PhNHCS		C ₆₄ H ₇₉ N ₉ O ₁₈ S ₂
297237	CO2H	H	HCl	C ₅₁ H ₆₂ N ₈ O ₁₅ S.HCl
297238	H	H	HCl	C ₅₀ H ₆₂ N ₈ O ₁₃ S.HCl



297234: C57 H68 N8 O16 S2

SOURCE – Bayer.

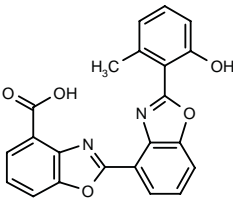
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AJI-9561

299165

2'-(2-Hydroxy-6-methylphenyl)-2,4'-bi-1,3-benzoxazole-4-carboxylic acid



C22 H14 N2 O5; Mol wt: 386.3616

ACTION – Cytotoxic benzoxazole derivative isolated from the mycelial extract of *Streptomyces* sp. AJ9561 and structurally related to UK-1, a natural topoisomerase II inhibitor. Compound showed cytotoxic activity against Jurkat and P388 cells (IC₅₀ = 0.88 and 1.63 μM) and may also act by inhibiting topoisomerase II.

SOURCE – Ajinomoto.

REFERENCES

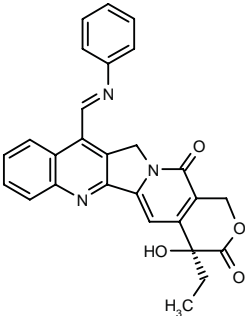
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CPT-154

299780

4(S)-Ethyl-4-hydroxy-11-[(E)-(phenylimino)methyl]-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione

7-(Phenyliminomethyl)camptothecin



C27 H21 N3 O4; Mol wt: 451.4799

ACTION – Antineoplastic agent, a 7-iminomethyl derivative of camptothecin with improved cytotoxic activity against non-small lung carcinoma H460 cells compared to topotecan (IC₅₀ = 0.13 and 1.38 μM, respectively). *In vivo*, compound showed efficacy comparable to topotecan against H460 xenografts in nude mice, providing dose-dependent tumor growth inhibition at 2-18 mg/kg p.o.

SOURCES – Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan (IT); Sigma-Tau.

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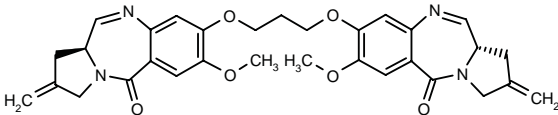
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SJG-136

287328

(11a*S*,11'a*S*)-8,8'-(1,3-Propanediyl)bis(oxy)bis(7-methoxy-2-methylene-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-one)

NSC-D694501
UP-2001



C31 H32 N4 O6; Mol wt: 556.6158

ACTION – Novel sequence-selective pyrrolobenzodiazepine dimer that acts as a highly efficient minor groove interstrand DNA crosslinking agent ($XL_{50} = 0.045 \mu M$). Compound arrested the cell cycle at the G2 phase and did not inhibit topoisomerase I or II. *In vitro*, it exhibited extremely potent cytotoxic activity against human ovarian cancer SK-OV-3, A2780 and CH1 cell lines ($IC_{50} = 9.1, 0.0225$ and 0.12 nM , respectively) including the cisplatin-resistant lines A2780*cisR* and CH1*cisR* ($IC_{50} = 0.024$ and 0.6 nM , respectively). Moreover, compound exhibited selective cytotoxicity in the NCI 60 cell line screen, and showed significant antitumor activity in the hollow fiber assay and against human tumor xenografts including human CNS tumor SF-295. Selected for further development.

SOURCES – University College London, London (GB); National Cancer Institute, Bethesda, MD (US); University of Nottingham, Nottingham (GB); University of Portsmouth, Portsmouth (GB).

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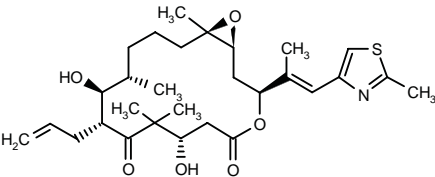
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ANTIMITOTIC DRUGS

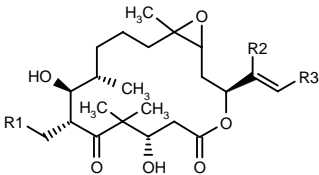
296730

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-10-Allyl-7,11-dihydroxy-8,8,12,16-tetramethyl-3-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione



C29 H43 N O6 S; Mol wt: 533.7257

ACTION – Antineoplastic agent that interacts with tubulin by stabilizing formed microtubules. Compound is potentially useful in the treatment of malignant tumors such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma and acute lymphocytic and myelocytic leukemia. It is also reported to be useful for antiangiogenesis therapy, as well as in the treatment of chronic inflammatory diseases such as psoriasis, multiple sclerosis and arthritis. *In vitro*, compound exhibited IC_{50} values of 1.2 and 3.6 nM, respectively, against breast carcinoma MCF-7 and multidrug-resistant NCI/ADR carcinoma cells, being more potent than paclitaxel ($IC_{50} = 3.5$ and $> 100 \text{ nM}$, respectively). Other exemplified compounds from this series of 6-alkenyl, 6-alkinyl and 6-epoxy-epothilone derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
296731	ethynyl-CH2	Me	2-Pyr	1 <i>S</i> ,16 <i>R</i>	C ₃₁ H ₄₃ NO ₆
296732	allyl	Me	2-Pyr	1 <i>S</i> ,16 <i>R</i>	C ₃₁ H ₄₅ NO ₆
296733	ethynyl	F	2-Me-4-thiazolyl	1 <i>S</i> ,16 <i>R</i>	C ₂₈ H ₃₈ FNO ₆ S
296734	ethynyl	F	2-Me-4-thiazolyl	1 <i>R</i> ,16 <i>S</i>	C ₂₈ H ₃₈ FNO ₆ S

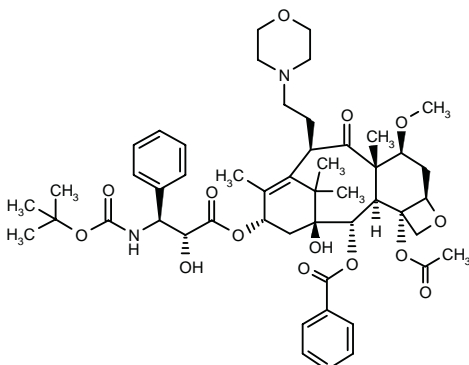
SOURCE – Schering AG.

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299805

[2a*R*]-[2a α ,4 β ,4a β ,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12a α ,12 β]-12b-Acetoxy-12-benzoyloxy-9-[3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenylpropionyloxy]-11-hydroxy-4-methoxy-4a,8,13,13-tetramethyl-6-[2-(4-morpholinyl)ethyl]-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C50 H66 N2 O14; Mol wt: 919.0714

ACTION – Orally active docetaxel analogue with higher cytotoxic activity against human small cell lung cancer PC-6 and non-small cell lung cancer PC-12 cells (IC₅₀ = 0.266 and 0.756 ng/ml, respectively, vs. 0.408-2.55 and 11.7-72.7 ng/ml, respectively, for docetaxel). Compound was also more active than docetaxel against vincristine-resistant PC-6 cells expressing P-glycoprotein (IC₅₀ = 9.01 ng/ml vs. 39.6-230 ng/ml). *In vivo*, it exerted potent oral antitumor activity against melanoma B16BL6 implanted s.c. in mice, inducing 98.3% tumor regression at a dose of 75 mg/kg, compared with no activity for docetaxel at 600 mg/kg p.o.

SOURCE – Daiichi Pharmaceutical.

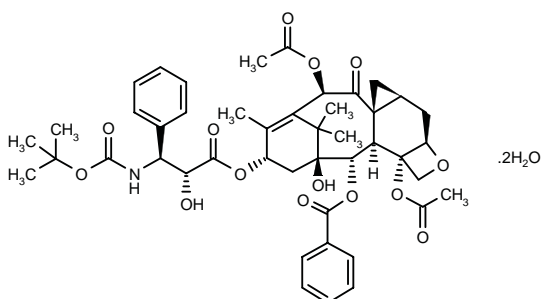
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RPR-109881A*

203141

(2a*R*,3a*R*,4a*R*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-Diacetoxy-9-[3(*S*)-(tert-butoxycarbonylamino)-2(*R*)-hydroxy-3-phenylpropionyloxy]-12-benzoyloxy-11-hydroxy-8,13,13-trimethyl-2a,3,3a,4,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]-cyclopropa[4,5]benz[1,2-*b*]oxet-5-one dihydrate



C45 H53 N O14 · 2H2O; Mol wt: 867.9363

ACTION – Semisynthetic taxoid, an antimitotic agent with a mechanism of action similar to docetaxel. Compound showed a broad spectrum of activity including docetaxel-sensitive murine melanoma B16, colon adenocarcinoma C38, breast carcinoma 13/C and pancreatic ductal adenocarcinoma P03 cells, as well as docetaxel-resistant P388 leukemia. In addition, it was active against human breast cancer Calc18 and colon cancer HCT-8 cells. It is only minimally recognized by P-glycoprotein, suggesting that it may be active against multidrug-resistant tumors. Currently undergoing clinical trials in North America, Europe and Japan.

SOURCE – Aventis Pharma.

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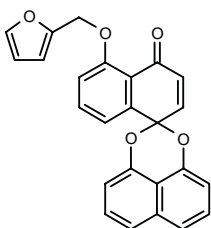
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*Identified compound **203141** Drug Data Rep 1994, 016(05): 0493.

SR-7

299920

5-(2-Furylmethoxy)spiro[1,4-dihydronaphthalene-1(4H), 2'-naphtho[1,8-de][1,3]dioxin]-4-one



C25 H16 O5; Mol wt: 396.3964

ACTION – Palmarumycin analogue with antiproliferative activity against both estrogen receptor-positive, *p53*-replete human breast carcinoma MCF-7 cells and estrogen receptor-negative, *p53*-deficient MDA-MB-231 cells (IC_{50} = 1.13 and 2.44 μ M, respectively) and comparable potency to the parent compound palmarumycin CP₁ (IC_{50} = 0.96 and 2.61 μ M, respectively). Moreover, at a concentration of 3 μ M it induced 50% inhibition of the growth of virally transformed murine embryonic fibroblasts. In murine mammary carcinoma tsFT210 cells, compound blocked cell cycle transition in the G2/M phase but not the G1 phase, via a mechanism that appears to be independent of tubulin disruption. No significant crossresistance with paclitaxel was seen.

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

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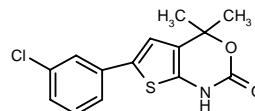
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HORMONAL AGENTS

296928

6-(3-Chlorophenyl)-4,4-dimethyl-2,4-dihydro-1H-thieno[2,3-d][1,3]oxazin-2-one



C14 H12 Cl N O2 S; Mol wt: 293.7728

ACTION – Progesterone receptor modulator, a specifically claimed compound from a series of cyclocarbamate and cyclic amide derivatives that acts as an agonist and/or antagonist at this receptor. Potentially useful for the treatment of uterine myometrial fibrosis, endometriosis, benign prostatic hypertrophy and hormone-dependent tumors, and as a contraceptive.

SOURCES – American Home Products; Ligand.

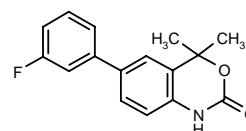
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296929

6-(3-Fluorophenyl)-4,4-dimethyl-2,4-dihydro-1H-3,1-benzoxazin-2-one



C16 H14 F N O2; Mol wt: 271.2896

ACTION – Progesterone receptor modulator, a representative compound from a series of cyclocarbamate derivatives that acts as a progesterone antagonist. Potentially useful for the treatment of uterine myometrial fibrosis, endometriosis, benign prostatic hypertrophy and hormone-dependent tumors.

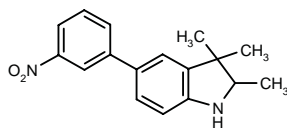
SOURCES – American Home Products; Ligand.

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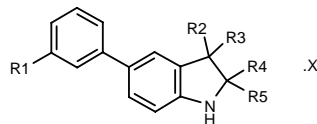
296930

2,3,3-Trimethyl-5-(3-nitrophenyl)-2,3-dihydro-1*H*-indole



C17 H18 N2 O2; Mol wt: 282.3412

ACTION – Progesterone receptor modulator that acts as a progesterone antagonist. Potentially useful for the treatment of uterine myometrial fibrosis, endometriosis, benign prostatic hypertrophy and hormone-dependent tumors. Other specifically claimed 3,3-substituted indoline derivatives are:



Compound	R1	R2	R3	R4	R5	X	Isomer	Formula
296931	NO2	Me	Me	Me	H	HCl		C ₁₇ H ₁₈ N ₂ O ₂ .HCl
296932	NO2	Me	Me	Me	H		R	C ₁₇ H ₁₈ N ₂ O ₂
296933	NO2	Me	Me	Me	H		S	C ₁₇ H ₁₈ N ₂ O ₂
296934	NO2	Et	Et	Et	Me			C ₂₁ H ₂₆ N ₂ O ₂
296935	NO2	Me	-(CH2)4-		H			C ₁₉ H ₂₀ N ₂ O ₂
296936	NO2	-(CH2)5-	Me		H			C ₂₀ H ₂₂ N ₂ O ₂
296937	NO2	Me	Me	H	H			C ₁₆ H ₁₆ N ₂ O ₂
296938	Cl	-(CH2)5-		H	H			C ₁₉ H ₂₀ ClN
296939	CN	Me	Me	Me	H			C ₁₈ H ₁₈ N ₂

SOURCES – American Home Products; Ligand.

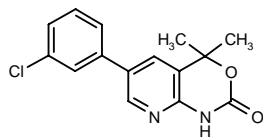
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2. Ullrich, J.W. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *3,3-Substd. indoline derivs*. WO 0066554.

296947

6-(3-Chlorophenyl)-4,4-dimethyl-2,4-dihydro-1*H*-pyrido-[2,3-*d*][1,3]oxazin-2-one



C15 H13 Cl N2 O2; Mol wt: 288.7327

ACTION – Progesterone receptor modulator, a specifically claimed compound from a series of cyclic urea and cyclic amide derivatives that acts as an agonist and/or antagonist at this receptor. Potentially useful for the treatment of uterine myometrial fibrosis, endometriosis, benign prostatic hypertrophy and hormone-dependent tumors.

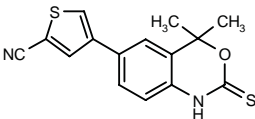
SOURCES – American Home Products; Ligand.

REFERENCES

1. Zhang, P. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Cyclic urea and cyclic amide derivs*. WO 0066592.

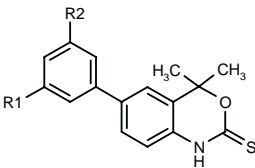
296949

4-(4,4-Dimethyl-2-thioxo-2,4-dihydro-1*H*-3,1-benzoxazin-6-yl)thiophene-2-carbonitrile



C15 H12 N2 O S2; Mol wt: 300.4048

ACTION – Progesterone receptor modulator that acts as a progesterone agonist and is potentially useful for the treatment of uterine myometrial fibrosis, endometriosis, benign prostatic hypertrophy and hormone-dependent tumors. Other exemplified cyclothiocarbamate derivatives include the following:



Compound	R1	R2	Formula
296951	Cl	H	C ₁₆ H ₁₄ ClNOS
296952	CN	F	C ₁₇ H ₁₃ FN ₂ OS
296955	CN	H	C ₁₇ H ₁₄ N ₂ OS

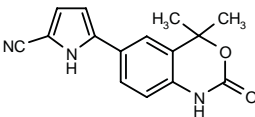
SOURCES – American Home Products; Ligand.

REFERENCES

1. Zhang, P. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Cyclothiocarbamate derivs. as progesterone receptor modulators*. WO 0066570.

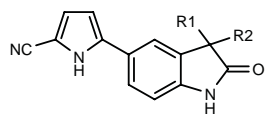
296956

5-(4,4-Dimethyl-2-oxo-2,4-dihydro-1*H*-3,1-benzoxazin-6-yl)-1*H*-pyrrole-2-carbonitrile



C15 H13 N3 O2; Mol wt: 267.2867

ACTION – Progesterone receptor modulator that acts as a progesterone agonist and is potentially useful for the treatment of uterine myometrial fibrosis, endometriosis, benign prostatic hypertrophy and hormone-dependent tumors. Other exemplified cyanopyrroles include the following:



Compound	R1	R2	Formula
296957	-(CH2)5-		C ₁₈ H ₁₇ N ₃ O
296958	Me	Me	C ₁₅ H ₁₃ N ₃ O
296959	-(CH2)4-		C ₁₇ H ₁₅ N ₃ O

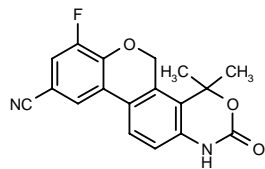
SOURCES – American Home Products; Ligand.

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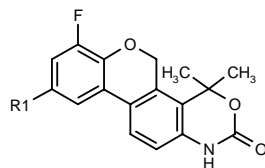
296960

7-Fluoro-4,4-dimethyl-2-oxo-1,2,4,5-tetrahydro-1-benzopyran[3,4-*f*][3,1]benzoxazine-9-carbonitrile



C18 H13 F N2 O3; Mol wt: 324.3097

ACTION – Progesterone receptor modulator that acts as an agonist and/or antagonist at this receptor. Potentially useful for the treatment of uterine myometrial fibrosis, endometriosis, benign prostatic hypertrophy and hormone-dependent tumors. Other exemplified tetracyclic compounds include the following:



Compound	R1	Formula
296961	H	C ₁₇ H ₁₄ FNO ₃
296962	Br	C ₁₇ H ₁₃ BrFNO ₃
296964	CHO	C ₁₈ H ₁₄ FNO ₄
296965	C(=NH)OH	C ₁₈ H ₁₅ FN ₂ O ₄

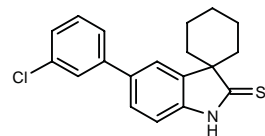
SOURCES – American Home Products; Ligand.

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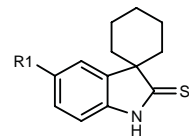
296966

5'-(3-Chlorophenyl)-2',3'-dihydrospiro[cyclohexane-1,3'-1'*H*-indole]-2'-thione



C19 H18 Cl N S; Mol wt: 327.8772

ACTION – Progesterone receptor modulator that acts as a progesterone agonist and is particularly useful for the treatment of progesterone-related carcinomas and adeno-carcinomas. Other exemplified thioxindoles include the following:



Compound	R1	Formula
296967	3-CN-Ph	C ₂₀ H ₁₈ N ₂ S
296968	5-CN-3-thienyl	C ₁₈ H ₁₆ N ₂ S ₂
296969	3-CN-5-F-Ph	C ₂₀ H ₁₇ FN ₂ S
296970	5-(CSNH2)-3-Me-2-thienyl	C ₁₉ H ₂₀ N ₂ S ₃

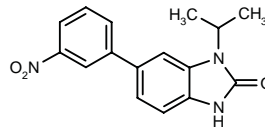
SOURCES – American Home Products; Ligand.

REFERENCES

1. Fensome, A. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Thio-oxindole derivs*. WO 0066555.

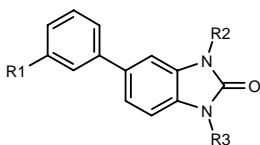
296972

1-Isopropyl-6-(3-nitrophenyl)-2,3-dihydro-1 *H*-benzimidazol-2-one



C16 H15 N3 O3; Mol wt: 297.3125

ACTION – Progesterone receptor modulator with progesterone antagonist and/or agonist activity that is particularly useful for the treatment of progesterone-related carcinomas and adenocarcinomas. Other exemplified benzimidazolones and analogues include the following:



Compound	R1	R2	R3	Formula
296974	Cl	CH2Ph	H	C ₂₀ H ₁₅ ClN ₂ O
296975	NO2	CH2Ph	H	C ₂₀ H ₁₅ N ₃ O ₃
296977	Cl	Me	H	C ₁₄ H ₁₁ ClN ₂ O
296978	NO2	Me	H	C ₁₄ H ₁₁ N ₃ O ₃
296979	NO2	H	Me	C ₁₄ H ₁₁ N ₃ O ₃
296980	Cl	i-Pr	H	C ₁₆ H ₁₅ ClN ₂ O

SOURCES – American Home Products; Ligand.

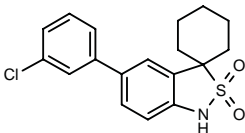
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1. Grubb, G.S. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Compsns. containing benzimidazolones and progestogens*. WO 0066168.

2. Zhang, P. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Benzimidazolones and analogues and their use as progesterone receptor ligands*. WO 0066564.

296982

5'-(3-Chlorophenyl)-1',3'-dihydrospiro[cyclohexane-1,3'-2',1'-benzisothiazole] 2',2'-dioxide



C18 H18 Cl N O2 S; Mol wt: 347.8642

ACTION – Progesterone receptor modulator, a specifically claimed compound from a series of 2,1-benzisothiazoline-2,2-dioxides that acts as a progesterone antagonist and is particularly useful for the treatment of progesterone-related carcinomas and adenocarcinomas and as a contraceptive.

SOURCES – American Home Products; Ligand.

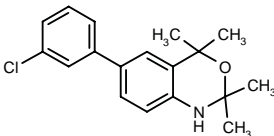
REFERENCES

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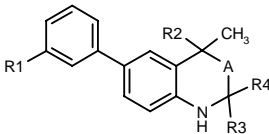
296983

6-(3-Chlorophenyl)-2,2,4,4-tetramethyl-2,4-dihydro-1H-3,1-benzoxazine



C18 H20 Cl N O; Mol wt: 301.8150

ACTION – Progesterone receptor modulator with progesterone-antagonist and/or -agonist activity that is particularly useful for the treatment of progesterone-related carcinomas and adenocarcinomas, as well as in contraceptive compositions. Other exemplified quinazoline and benzoxazine derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
296990	Cl	Me	Me	CF3	O	C ₁₈ H ₁₇ ClF ₃ NO
296991	NO2	H	Me	Me	O	C ₁₇ H ₁₈ N ₂ O ₃
296992	Cl	cyclopropyl	-O-	NH		C ₁₈ H ₁₇ ClN ₂ O
296994	Cl	cyclopropyl	-O-	N(Me)		C ₁₉ H ₁₉ ClN ₂ O
296995	Cl	Me	-O-	CH2		C ₁₇ H ₁₆ ClNO

SOURCES – American Home Products; Ligand.

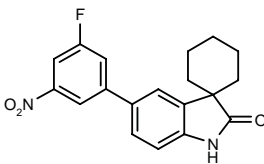
REFERENCES

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2. Zhang, P. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Quinazolinone and benzoxazine derivs. as progesterone receptor modulators*. WO 0066560.

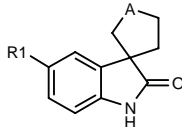
296997

5'-(3-Fluoro-5-nitrophenyl)-2',3'-dihydrospiro[cyclohexane-1,3-1'H-indol]-2'-one



C19 H17 F N2 O3; Mol wt: 340.3523

ACTION – Progesterone receptor modulator that acts as a progesterone antagonist and is particularly useful for the treatment of progesterone-related carcinomas and adenocarcinomas, and as a contraceptive. Other exemplified indoline derivatives include the following:



Compound	R1	A	Formula
296999	5-CN-3-thienyl	-(CH2)2-	C ₁₈ H ₁₆ N ₂ OS
297000	5-CN-2-thienyl	-(CH2)2-	C ₁₈ H ₁₆ N ₂ OS
297001	3-CN-5-F-Ph	-CH2-	C ₁₉ H ₁₅ FN ₂ O
297002	3-CN-Ph	-CH2-	C ₁₉ H ₁₆ N ₂ O
297003	5-NO2-2-pyrrolyl	-(CH2)2-	C ₁₇ H ₁₇ N ₃ O ₃
297004	5-CN-3-Me-2-thienyl	-CH2-	C ₁₈ H ₁₆ N ₂ OS
297005	5-CN-3-Me-2-thienyl	-(CH2)2-	C ₁₉ H ₁₈ N ₂ OS
297006	3-CN-Ph	-(CH2)2-	C ₂₀ H ₁₈ N ₂ O

SOURCES – American Home Products; Ligand.

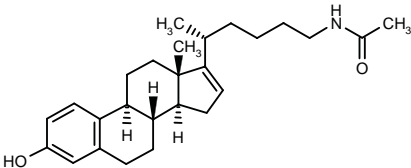
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2. Grubb, G.S. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Contraceptive compsns. containing indoline derivs. and progestational agents*. WO 0066167.

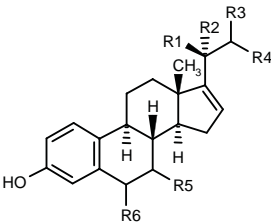
297444

N-[5(R)-[3-Hydroxyestra-1,3,5(10),16-tetraen-17-yl]-hexyl]acetamide



C26 H37 N O2; Mol wt: 395.5833

ACTION – Agent for the treatment of disorders involving abnormal cell proliferation, particularly cancer, and for promoting wound and burn healing, a representative compound from a series of steroid derivatives with a C17-alkyl side chain and an aromatic A-ring that exhibit potent effects on cell growth and differentiation and have low calcemic activity. Compound is also reported to promote the healing of mouse ear pouches *in vivo*. In addition, it has been shown to bind to estrogen receptors, while being free from uterotrophic effects, and is therefore expected to be of further use in the treatment and prevention of osteoporosis and for reducing serum cholesterol. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
297447	H	Me	H	(CH2)3NHCOCH2Ph	H	H	C ₃₂ H ₄₁ NO ₂
297449	Me	H	H	ethynyl-C(Et)2NH2	H	H	C ₂₈ H ₃₉ NO
297450	Me	H	OH	ethynyl-C(Et)2NH2	H	H	C ₂₈ H ₃₉ NO ₂
297451	Me	H	H	ethynyl-CH2OH	H	H	C ₂₄ H ₃₀ O ₂
297452	Me	H	H	(CH2)3NHAc	bond		C ₂₆ H ₃₅ NO ₂

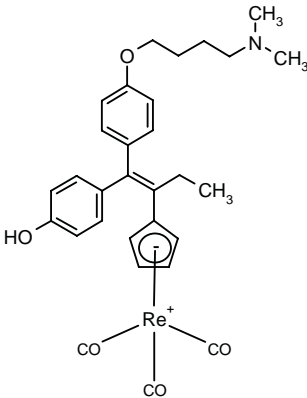
SOURCE – Research Institute for Medicine & Chemistry.

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1. Marsden, J.C. et al. (Research Institute for Medicine & Chemistry, Inc.) *Steroid cpds. with a C17-alkyl side chain and an aromatic A-ring for use in therapy*. WO 0068246.

299653

(Tricarbonyl)[(1,2,3,4,5-η)-3-[1-(4-hydroxyphenyl)-1-[4-(4-(dimethylamino)butoxy]phenyl)-1-buten-2-yl]-2,4-cyclopentadien-1-yl]rhenium



C27 H32 N O2 . 3 C O . Re; Mol wt: 672.7948

ACTION – Organometallic complex based on the tamoxifen skeleton with antiestrogenic/antiproliferative activity similar to hydroxytamoxifen on breast cancer MVLN and MDA-MB-231 cells. The presence of rhenium is considered an advantage for its development as a radio-pharmaceutical for the treatment of breast cancer.

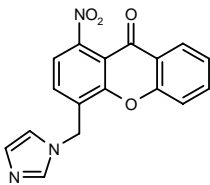
SOURCES – Ecole Nationale Supérieure de Chimie de Paris, Paris (FR); Institut Jules Bordet, Brussels (BE).

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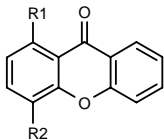
300249

4-(1*H*-Imidazol-1-ylmethyl)-1-nitro-9*H*-xanthen-9-one



C17 H13 N3 O4; Mol wt: 323.3067

ACTION – Nonsteroidal aromatase inhibitor (IC₅₀ = 0.04 μM against human enzyme) with slightly superior potency compared to fadrozole (IC₅₀ = 0.052 μM) and good selectivity relative to 17α-hydroxylase/C_{17,20}-lyase (P-450 17). Potential lead compound for the development of agents for the treatment of androgen-dependent diseases such as breast cancer. Other related xanthone derivatives include the following:



Compound	R1	R2	Formula
300085	CN	1-imidazolyl-CH2	C ₁₈ H ₁₁ N ₃ O ₂
300086	1-imidazolyl-CH2	Br	C ₁₇ H ₁₁ BrN ₂ O ₂

SOURCES – Università degli Studi di Bologna, Bologna, (IT); Universität des Saarlandes, Saarbrücken (DE).

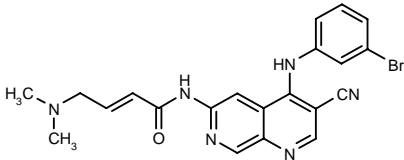
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

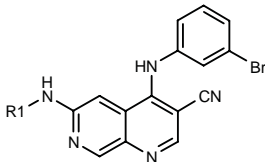
296637

N-[4-(3-Bromophenylamino)-3-cyano-1,7-naphthyridin-6-yl]-4-(dimethylamino)-2(*E*)-butenamide



C21 H19 Br N6 O; Mol wt: 451.3261

ACTION – Agent for the treatment of cancer and polycystic kidney disease, an inhibitor of protein tyrosine kinases such as epidermal growth factor (EGF) receptor tyrosine kinase (IC₅₀ = 0.005 μM using recombinant enzyme). *In vitro*, compound was shown to inhibit the growth of human breast cancer MDA-MB-435, SK-BR-3, 3T3 and Her2Neu, human epidermoid carcinoma A-431 and human colon cancer SW620 cells with respective IC₅₀ values of 0.4635, 0.03565, 0.2716, 0.04359, 0.08798 and 0.356 μg/ml. Other compounds from this series of substituted 3-cyano[1,7], [1,5] and [1,8]naphthyridine derivatives include the following:



Compound	R1	Formula
296640	1-propynyl-CO	C ₁₉ H ₁₂ BrN ₅ O
296642	Me	C ₁₆ H ₁₂ BrN ₅

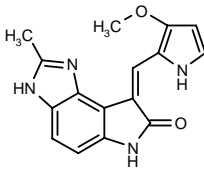
SOURCE – American Home Products.

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1. Wissner, A. et al. (American Cyanamid Co.) *Substd. 3-cyano-[1.7], [1.5], and [1.8]-naphthyridine inhibitors of tyrosine kinases*. WO 0066583.

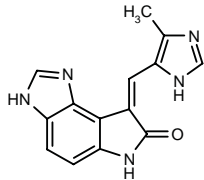
297045

(8*Z*)-2-Methyl-8-(3-methoxy-1 *H*-pyrrol-2-ylmethylene)-3,6,7,8-tetrahydropyrrolo[3,2-*e*]benzimidazol-7-one



C16 H14 N4 O2; Mol wt: 294.3126

ACTION – Antiproliferative agent, an inhibitor of cyclin-dependent kinases, particularly CDK2, with antiproliferative activity in the estrogen receptor-negative epithelial breast carcinoma line MDA-MB-435 (IC₅₀ < 3.5 μM). Particularly useful for the treatment of cancer, preferably for solid tumors such as breast or colon tumors. Another representative compound from this series of 4,5-azolo-oxindoles is:



297046: C14 H11 N5 O

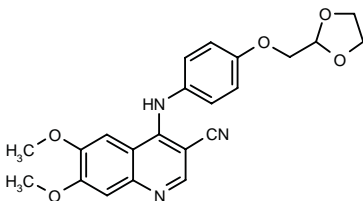
SOURCE – Roche.

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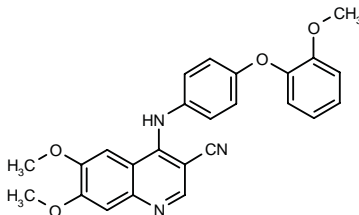
297074

4-[4-(1,3-Dioxolan-2-ylmethoxy)phenylamino]-6,7-dimethoxyquinoline-3-carbonitrile



C22 H21 N3 O5; Mol wt: 407.4239

ACTION – Agent for the treatment of hyperproliferative diseases, particularly cancer, with MEK-inhibitory activity. *In vitro*, compound inhibited the activation of MAP kinase by MEK with an IC₅₀ value of 0.15 μM. Another exemplified compound from this series of quinoline derivatives is:



297075: C25 H21 N3 O4

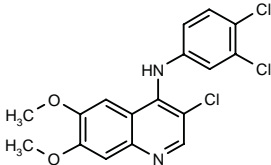
SOURCE – AstraZeneca.

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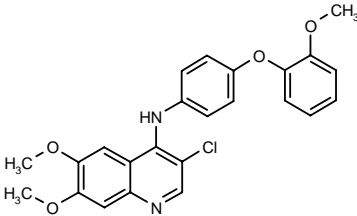
297076

3-Chloro-*N*-(3,4-dichlorophenyl)-6,7-dimethoxyquinolin-4-amine



C17 H13 Cl3 N2 O2; Mol wt: 383.6607

ACTION – Agent for the treatment of hyperproliferative diseases, particularly cancer, with MEK-inhibitory activity. *In vitro*, compound inhibited the activation of MAP kinase by MEK with an IC₅₀ value of 1.53 μM. Another exemplified compound from this series of quinoline derivatives is:



297077: C24 H21 Cl N2 O4

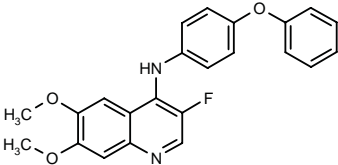
SOURCE – AstraZeneca.

REFERENCES

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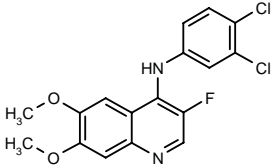
297078

3-Fluoro-6,7-dimethoxy-*N*-(4-phenoxyphenyl)quinolin-4-amine



C23 H19 F N2 O3; Mol wt: 390.4121

ACTION – Agent for the treatment of hyperproliferative diseases, particularly cancer, with MEK-inhibitory activity. *In vitro*, compound inhibited the activation of MAP kinase by MEK with an IC₅₀ value of 0.55 μM. Another exemplified compound from this series of quinoline derivatives is:



297079: C17 H13 Cl2 F N2 O2

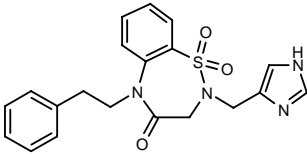
SOURCE – AstraZeneca.

REFERENCES

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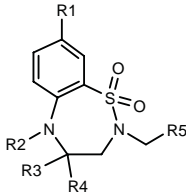
297262

2-(1 *H*-Imidazol-4-ylmethyl)-5-(2-phenylethyl)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-4-one 1,1-dioxide



C20 H20 N4 O3 S; Mol wt: 396.4690

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds from this series of 1,2,5-benzothiadiazepine-1,1-dioxides *N*-substituted with an imidazolylalkyl group are:



Compound	R1	R2	R3	R4	R5	Formula
297263	H	CH2CH2Ph	-O-		1-Me-5-imidazolyl	C ₂₁ H ₂₂ N ₄ O ₃ S
297265	H	CH2Ph	-O-		4-imidazolyl	C ₁₉ H ₁₈ N ₄ O ₃ S
297266	H	(S)-CH(Ph)-CO2Et	-O-		4-imidazolyl	C ₂₁ H ₂₀ N ₄ O ₅ S
297267	H	(S)-CH(Ph)-CH2OH	H	H	4-imidazolyl	C ₂₀ H ₂₂ N ₄ O ₃ S
297272	H	CH2Ph	H	H	4-imidazolyl	C ₁₉ H ₂₀ N ₄ O ₂ S
297273	H	CH2CH2Ph	H	H	4-imidazolyl	C ₂₀ H ₂₂ N ₄ O ₂ S
297275	H	2-MeO-PhCH2	H	H	4-imidazolyl	C ₂₀ H ₂₂ N ₄ O ₃ S
297277	Br	CH2Ph	H	H	4-imidazolyl	C ₁₉ H ₁₉ BrN ₄ O ₂ S
297278	H	3-MeO-PhCH2	H	H	4-imidazolyl	C ₂₀ H ₂₂ N ₄ O ₃ S
297279	H	H	H	H	4-imidazolyl	C ₁₂ H ₁₄ N ₄ O ₂ S
297281	H	CH2Ph	H	H	2-imidazolyl-CH2	C ₂₀ H ₂₂ N ₄ O ₂ S
297282	H	CH2Ph	H	H	4-imidazolyl-CH2	C ₂₀ H ₂₂ N ₄ O ₂ S

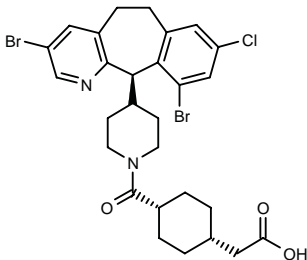
SOURCE – Bristol-Myers Squibb.

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1. Leftheris, K. et al. (Bristol-Myers Squibb Co.) *1,2,5-Benzothiadiazepine-1,1-dioxides with N-2 imidazolylalkyl substituents*. US 6156746.

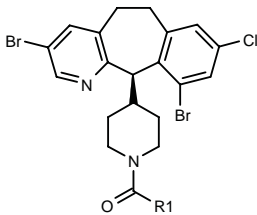
297406

cis-2-[4-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-ylcarbonyl]cyclohexyl]acetic acid



C28 H31 Br2 Cl N2 O3; Mol wt: 638.8249

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC₅₀ = 0.0033 μM) proven to inhibit Ras processing in COS cells (IC₅₀ = 0.07 μM). Other specifically claimed tricyclic compounds are:



Compound	R1	Formula
297407	3-CO2Me-cyclobutyl	C ₂₆ H ₂₇ Br ₂ ClN ₂ O ₃
297408	trans-4-(CO2HCH2)-cyclohexyl	C ₂₈ H ₃₁ Br ₂ ClN ₂ O ₃

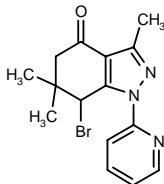
SOURCE – Schering-Plough.

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1. Guzi, T.J. and Rane, D.F. (Schering Corp.) *Farnesyl protein transferase inhibitors*. US 6159984.

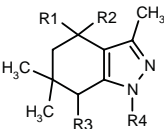
297756

7-Bromo-3,6,6-trimethyl-1-(2-pyridinyl)-4,5,6,7-tetrahydro-1*H*-indazol-4-one



C15 H16 Br N3 O; Mol wt: 334.2154

ACTION – Agent for the treatment of cancer and other proliferative diseases such as psoriasis, vascular smooth muscle cell proliferation associated with atherosclerosis and postsurgical stenosis and restenosis, as well as for the treatment of Alzheimer’s disease, that exhibits cyclin-dependent kinase (CDK)/cyclin-inhibitory activity. Other specifically claimed compounds from this series of 4,5,6,7-tetrahydroindazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
297757	-O-		F	2-Pyr	C ₁₅ H ₁₆ FN ₃ O
297758	-O-		OH	2-Pyr	C ₁₅ H ₁₇ N ₃ O ₂
297759	-O-		SPh	2-Pyr	C ₂₁ H ₂₁ N ₃ OS
297760	-N(OH)-		H	2-Pyr	C ₁₅ H ₁₈ N ₄ O
297761	-N(OH)-		OEt	2-Pyr	C ₁₇ H ₂₂ N ₄ O ₂
297762	OMe	H	H	2-Pyr	C ₁₆ H ₂₁ N ₃ O
297763	-O-		H	3-NO2-Ph	C ₁₆ H ₁₇ N ₃ O ₃
297764	-O-		H	CONH2	C ₁₁ H ₁₅ N ₃ O ₂

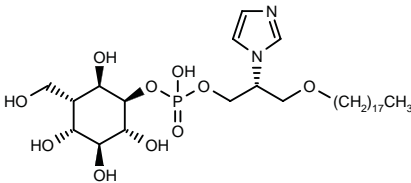
SOURCE – Pharmacia.

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299205

2(*R*)-(1*H*-imidazol-1-yl)-3-(octadecyloxy)propyl (1*R*,2*R*,3*S*,4*R*,5*S*,6*R*)-2,3,4,6-tetrahydroxy-5-(hydroxy-methyl)cyclohexyl hydrogen phosphate



C31 H59 N2 O10 P; Mol wt: 650.7851

ACTION – Phosphatidylinositol (PI) analogue able to inhibit both PI 3-kinase and the protein kinase Akt (IC₅₀ = 7.9 and 20.5 μM, respectively), as well as to block the growth of cancer cell lines including murine NIH3T3 fibroblasts, human colon adenocarcinoma HT-29 and breast carcinoma MCF-7 cell lines (IC₅₀ = 8.2, 6.5 and 2.0 μM, respectively). Potentially useful for the selective control of cancer cell growth.

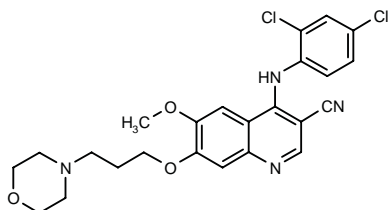
SOURCES – Arizona Cancer Center, Tucson, AZ (US); Georgetown University, Washington, DC (US).

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300077

4-(2,4-Dichlorophenylamino)-6-methoxy-7-[3-(4-morpholinyl)propoxy]quinoline-3-carbonitrile



C24 H24 Cl2 N4 O3; Mol wt: 487.3846

ACTION – Src kinase inhibitor (IC_{50} = 3.8 nM) with submicromolar inhibitory activity on the growth of Src-transformed rat fibroblasts in suspension (anchorage-independent assay; IC_{50} = 0.94 μ M). Compound also strongly inhibited the phosphorylation of cellular proteins in extracts from Src-transformed fibroblasts. Potentially useful for the treatment of diseases in which Src is overexpressed such as ovarian and colon tumors and osteoporosis.

SOURCE – Wyeth-Ayerst.

REFERENCES

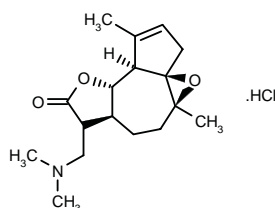
1. Boschelli, D.H. et al. *Synthesis and Src kinase inhibitory activity of a series of 4-phenylamino-3-quinolinecarbonitriles*. J Med Chem 2001, 44(5): 822.

ARGLABIN-DMA.HCl

298269

(3a*R*,4a*S*,6a*S*,9a*S*,9b*R*)-7-(Dimethylaminomethyl)-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3*H*-oxireno[8,8a]-azuleno[4,5-*b*]furan-8(4a*H*)-one hydrochloride

Dimethylaminoarglabin hydrochloride



C17 H25 N O3 . HCl; Mol wt: 327.8494

ACTION – Synthetic analogue of arglabin⁺, a sesquiterpene γ -lactone isolated from the Kazakstan plant *Artemisia glabella*, proven to competitively inhibit farnesyl diphosphate binding to protein farnesyltransferase (IC_{50} = 25 μ M or less), as well as Ras protein posttranslational modification in cells. In addition, compound inhibited the anchorage-dependent proliferation of neuroblastoma cells (IC_{50} = 10 μ g/ml) and the anchorage-independent growth of neuroblastoma and virally transformed kidney cells with comparable potency. It inhibited the growth of a range of primary human tumor cells (median IC_{50} = 2.2 μ g/ml), with higher activity against breast cancer cells (IC_{50} = 1.74 μ g/ml).

SOURCES – Institute of Phytochemistry, Kazakstan, Karaganda (KZ); NuOncology Labs.

REFERENCES

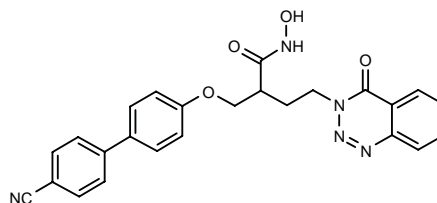
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3. Adekenov, S.M. (Paracure, Inc.) *Pharmaceutical compsns. of arglabin and arglabin derivs*. US 5902809, WO 9848789.
4. Shaikenov, T.E. (International Phytochemistry Research Laboratory Ltd.) *Farnesyl-protein transferase inhibitors*. WO 9943314.
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*Drug Data Reo 1999, 021(09): 0829.

ANGIOGENESIS INHIBITORS

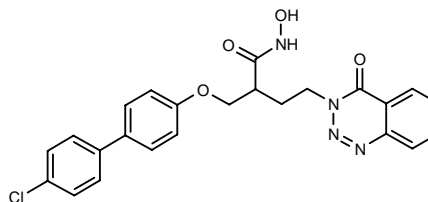
299784

2-(4'-Cyanobiphenyl-4-yloxymethyl)-4-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)butyrohydroxamic acid



C25 H21 N5 O4; Mol wt: 455.4719

ACTION – Matrix metalloproteinase (MMP) inhibitor with high selectivity for gelatinase A (MMP-2; IC_{50} = 0.4 nM) and B (MMP-9; IC_{50} = 0.6 nM), stromelysin 1 (MMP-3; IC_{50} = 1.1 nM) and collagenase 3 (MMP-13; IC_{50} = 0.6 nM) over interstitial collagenase (MMP-1; IC_{50} = 116 nM). In an *in vitro* model of MMP-dependent cartilage loss, compound was found to inhibit proteoglycan degradation with an IC_{50} value of 0.01 μ M. It showed good metabolic stability *in vitro* in hepatic microsomes and was predicted to have excellent absorption based on Caco-2 cell permeability. Preliminary evaluation in an experimental metastasis model in mice showed significant reductions in tumor burden of 35 and 40% at 100 and 200 mg/kg i.p., respectively. Another related compound is:



299785: C24 H21 Cl N4 O4

SOURCE – Servier.

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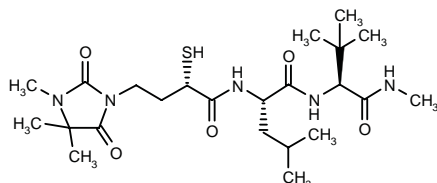
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BMS-275291*

251278

N-[2(S)-Sulfanyl-4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)butyryl]-L-leucyl-L-*tert*-leucine methylester

D-2163



C23 H41 N5 O5 S; Mol wt: 499.6729

ACTION – Orally active, broad-spectrum matrix metalloproteinase (MMP) inhibitor with nanomolar activity against MMP-1 (fibroblast collagenase), MMP-2 (gelatinase A), MMP-9 (gelatinase B) and MMP-14 (MT-1 MMP). When given to mice at doses of 10-90 mg/kg (2 h before and 2, 24, 48 and 72 h after tumor implantation), it was shown to dose-dependently reduce lung metastases in the B16BL6 model of experimental metastasis. In a murine angiogenesis model, compound induced a dose-dependent inhibition of endothelial cell migration into s.c.-implanted Matrigel plugs. A favorable pharmacokinetic profile was obtained in mice, with plasma concentrations exceeding the IC₅₀ values against MMP-2 and MMP-9. Compound is undergoing phase II/III studies in patients with advanced or metastatic non-small cell lung cancer.

SOURCES – Bristol-Myers Squibb; Celltech Group.

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14. *Major U.K. biopharmaceutical company merger announced*. DailyDrugNews.com (Daily Essentials) 1999, Nov 12.

15. *MMP inhibitor developed at Chiroscience enters clinical trials for cancer*. DailyDrugNews.com (Daily Essentials) 1998, Jan 5.

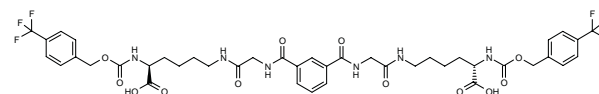
16. *New product pipeline*. Celltech Group plc Press Release 2000, March 22.

*Identified compound **251278** (see **251167**) Drug Data Rep 1997, 019(07): 0659.

TSRI-265

299745

N¹,N³-Bis[2-[5(S)-carboxy-5-[4-(trifluoromethyl)benzyl-oxycarboxamido]pentylamino]-2-oxoethyl]benzene-1,3-dicarboxamide



C42 H46 F6 N6 O12; Mol wt: 940.8434

ACTION – Antiangiogenic agent able to inhibit the binding and localization of the matrix metalloproteinase MMP-2 (gelatinase A) to the cell surface through binding to $\alpha_v\beta_3$ integrin. Compound did not inhibit the binding of vitronectin to integrin $\alpha_v\beta_3$, nor did it directly affect MMP-2 activation or catalytic activity, but it suppressed cell-mediated collagen degradation as a result of inhibition of the interaction of MMP-2 with $\alpha_v\beta_3$. *In vivo* in the chick chorioallantoic membrane (CAM) assay, compound (3 μ M) almost completely inhibited angiogenesis induced by basic fibroblast growth factor (bFGF), without suppressing MMP-2 activation. Moreover, compound significantly reduced the growth of $\alpha_v\beta_3$ -negative melanoma CS-1 following a single i.v. injection of approximately 10 μ g, apparently by reducing tumor vasculature, leading to cell death within the tumor.

SOURCE – Scripps Research Institute, La Jolla, CA (US).

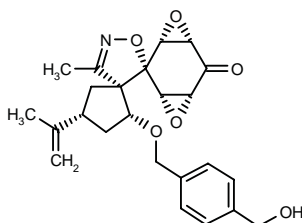
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OTHER ONCOLYTIC DRUGS

296725

(1''*S*,2*R*,2''*R*,3*S*,4''*R*,5*R*,6*S*)-2,3:5,6-Diepoxy-2''-[4-(hydroxymethyl)benzyloxy]-3'-methyl-4''-(1-methylvinyl)-dispiro[cyclohexane-1,5'-isoxazole-4'-1''-cyclopentan]-4-one



C24 H27 N O6; Mol wt: 425.4783

ACTION – Antiproliferative agent for the treatment of cancer, particularly leukemia, and psoriasis, a representative compound from a series of spirocyclic derivatives.

SOURCE – Schering AG.

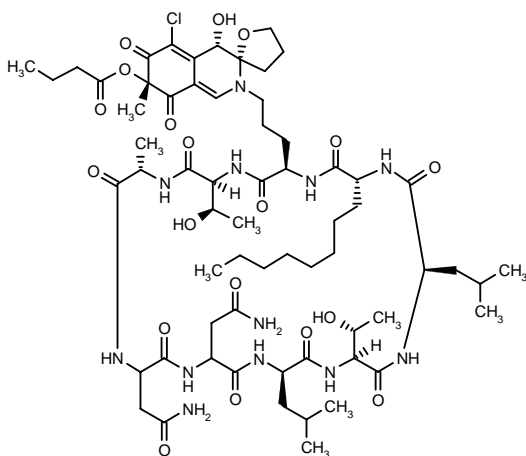
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CHLOROFUSIN

299910

(5*R*,8*S*,11*R*,14*R*,17*R*,20*S*,23*S*)-17-[3-[(3'*S*,4'*S*,7'*S*)-7'-(Butanoyloxy)-5'-chloro-4'-hydroxy-6',8'-dioxo-7'-methyl-2',3,4,4',6',7',8'-octahydrospiro[furan-2,3'-isoquinolin]-2'-yl]propyl]-8,20-bis[1(*R*)-hydroxyethyl]-5,11-diisobutyl-23-methyl-14-octyl-3,6,9,12,15,18,21,24,27-nonaoxo-17-propyl-1,4,7,10,13,16,19,22,25-nonaazacycloheptacosane-2,26-diacetamide



C63 H99 Cl N12 O19; Mol wt: 1363.9930

ACTION – Microbial metabolite produced by the fermentation of *Fusarium* sp. 22026, with the ability to antagonize the interaction between p53 phosphoprotein and the cellular protein MDM2 ($IC_{50} = 4.6 \mu M$). Compound did not modify the TNF- α /TNF- α receptor protein-protein interaction and it was devoid of cytotoxicity against HepG2 cells and antimicrobial activity against a range of microorganisms. Such a profile may be of interest in cancer therapy.

SOURCE – Cambridge Centre for Molecular Recognition, Cambridge (GB).

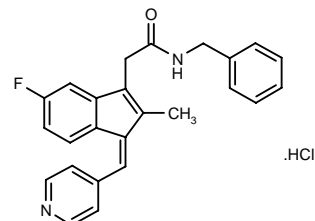
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CP-461*,2,4,9,10,12-16,18,20-28

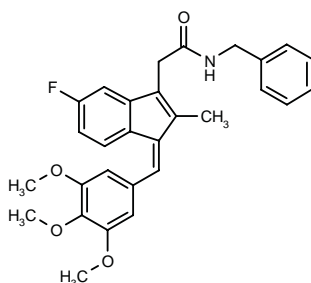
278044

N-Benzyl-2-[5-fluoro-2-methyl-1-[(*Z*)-(pyridin-4-yl)-methylene]-1*H*-inden-3-yl]acetamide hydrochloride



C25 H21 F N2 O . HCl; Mol wt: 420.9128

ACTION – Selective apoptotic antineoplastic agent, a potent derivative of exisulind which, similar to the parent compound, induces apoptosis via inhibition of cGMP phosphodiesterase ($IC_{50} = 3.5 \mu M$) and activation of cGMP-dependent protein kinase. Compound showed antiproliferative activity against a range of human breast cancer cell lines expressing low levels of HER2/neu receptors (MCF-7, MDA-MB-231, MDA-MB-435S, MDA-MB-436, BT-20) or cell lines overexpressing these receptors (BT-474, SR-BR-3, MDA-MB-453), with IC_{50} values of 0.5-0.9 μM . In addition, it induced apoptosis ($EC_{50} = 0.8 \mu M$) in both HER2/neu-overexpressing MDA-MB-453 cells and MCF-7 cells lacking these receptors. Synergistic effects in combination with both trastuzumab and docetaxel were seen in BT-474 cells with high-level expression of HER2/neu receptors. Compound was also active *in vitro* against leukemia and myeloma cell lines (K-562, CCRF-CEM, MOLT-4 and RPMI-8226 cells), with IC_{50} values of 1.18-1.8 μM . It significantly inhibited the growth of androgen-independent human prostate cancer PC-3 xenografts in nude mice at the dose of 18 mg/kg/day p.o. for 20 days) and it enhanced the antitumor effect of paclitaxel against human mammary MX-1 tumors implanted s.c. in nude mice. Phase I studies in healthy volunteers showed that compound is absorbed rapidly after oral administration and produces high plasma levels that exceed the concentration inducing apoptosis in cancer cells. Potentially useful as both a single agent and in combination regimens for the treatment of breast cancer. Another derivative of exisulind is:



CP-248 [260093]:**1-3-5-8,11,13,16,17,19,21 C29 H28 F N O4

SOURCE – Cell Pathways.

REFERENCES

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- Liu, L. et al. (Cell Pathways, Inc.) *Methods for identifying cpds. for inhibition of neoplastic lesions, and pharmaceutical compsns. containing such cpds..* EP 0997145.
- Menander, K.B. and Mayle, M.J. (Cell Pathways, Inc.) *A method for treating patients with acne by administering a cyclic GMP PDE inhibitor.* WO 0044372.
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- Pamukcu, R. and Menander, K.B. (Cell Pathways, Inc.) *Method for treating a patient with neoplasia by treatment with a pyrimidine analog.* WO 0027403.
- Pamukcu, R. and Menander, K.B. (Cell Pathways, Inc.) *Method for treating a patient with neoplasia by treatment with an anthracycline antibiotic.* WO 0027404.
- Piazza, G.A. et al. (Cell Pathways, Inc.) *Method for identifying cpds. for inhibition of cancerous lesions.* US 5858694.
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- Alila, H. et al. *A pharmacokinetic and safety study of a selective apoptotic antineoplastic drug (SAAND), CP461, in healthy volunteers.* Proc Am Soc Clin Oncol 2000, 19: Abst 817.
- Alila, H.W. et al. *Antineoplastic effects of exisulind (Prevatac™) and its analogs on leukemia and myeloma cell lines.* Proc Am Soc Clin Oncol 1999, 18: Abst 89.
- Alilla, H. et al. *CP-461 enhances the antitumor effects of paclitaxel in subcutaneously implanted human mammary tumor (MX-1) xenografts in nude mice.* Proc Amer Assoc Cancer Res 2000, 41: Abst 916.
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- Joe, A.K. et al. *Sulindac compounds inhibit growth, induce apoptosis, and enhance glutathione synthesis in Barrett's esophagus-derived cancer cells.* Proc Amer Assoc Cancer Res 2000, 41: Abst 3154.
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- Piazza, G.A. et al. *Selective apoptosis of human prostate tumor cells by exisulind and an analog via cyclooxygenase (COX)-independent pathway.* Proc Amer Assoc Cancer Res 1999, 40: Abst 27.
- Schiller, J. et al. *CP-461 is active alone and in combination with gemcitabine, vinorelbine, or irinotecan in non-small cell lung cancer cell lines.* Ann Oncol 2000, 11(Suppl. 4): Abst 661P.
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22. *Cell Pathways completes phase Ib trial of CP-461.* DailyDrugNews.com (Daily Essentials) 2000, Aug 7.

23. *Cell Pathways confirms novel mechanism of action of exisulind, CP-461 and related compounds.* DailyDrugNews.com (Daily Essentials) 1999, Jan 11.

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25. *Cell Pathways updates clinical status of SAANDs.* DailyDrugNews.com (Daily Essentials) 1999, June 7.

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27. *Phase Ia results reported for Cell Pathways' novel SAAND.* DailyDrugNews.com (Daily Essentials) 1999, Aug 10.

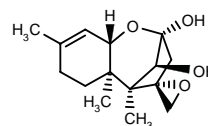
*Identified compound **278044** Drug Data Rep 1999, 021(07): 0652.

Identified compound **260093 Drug Data Rep 1998, 020(04): 0356.

CURVULAROL

299159

(2S,4S,5S,5aR,9aS,10S)-5,5a,8-Trimethyl-2,3,4,5,5a,6,7,9a-octahydrospiro[2,5-methano-1-benzoxepin-4,2'-oxiran]-2,10-diol



C15 H22 O4; Mol wt: 266.3348

ACTION – Antiproliferative agent isolated from the fermentation broth of *Curvularia* sp. RK97-F166, with no antibacterial or antifungal activity but strong cytotoxic activity against a panel of human cancer cells including erythroleukemia K-562, promonocytic leukemia U-937, promyelocytic leukemia HL-60 and small cell lung carcinoma H1299 cells (IC₅₀ = 55, 40, 40 and 75 ng/ml, respectively). At higher concentrations (IC₅₀ = 100-430 ng/ml) it was also active against human epitheloid carcinoma HeLa and v-src-transformed rat kidney NRK cells. Moreover, compound at 30 ng/ml induced reversion from transformed to normal morphology in src^{ts}-NRK cells, and at 50 ng/ml it induced cell cycle arrest at the G1 phase. Finally, it was more effective in inhibiting protein synthesis than DNA or RNA synthesis.

SOURCES – Institute of Physical and Chemical Research (RIKEN), Saitama (JP); Toyo University, Saitama (JP).

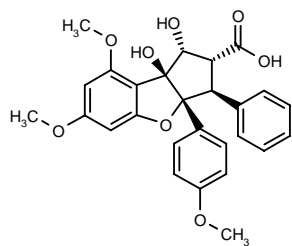
REFERENCES

- Honda, Y. et al. *Isolation, and biological properties of a new cell cycle inhibitor, curvularol, isolated from Curvularia sp. RK97-F166.* J Antibiot 2001, 54(1): 10.

ROCAGLOIC ACID

300028

(1*R*,2*R*,3*S*,3*aR*,8*bS*)-1,8*b*-Dihydroxy-6,8-dimethoxy-3*a*-(4-methoxyphenyl)-3-phenyl-2,3,3*a*,8*b*-tetrahydro-1*H*-cyclopenta[*b*][1]benzofuran-2-carboxylic acid



C27 H26 O8; Mol wt: 478.4944

ACTION – Bioactive compound extracted from the leaves of the Formosan plant *Aglaia elliptifolia* with cytotoxic activity against a panel of human cancer cells including lung adenocarcinoma A549, colon adenocarcinoma HT-29 and oral epidermoid carcinoma KB cells (IC₅₀ = 0.74, 0.74 and 0.84 ng/ml, respectively), as well as against murine lymphocytic leukemia P388 cells (IC₅₀ = 1.2 ng/ml).

SOURCES – Kaohsiung Medical College, Kaohsiung (TW); National Sun Yat-Sen University, Kaohsiung (TW).

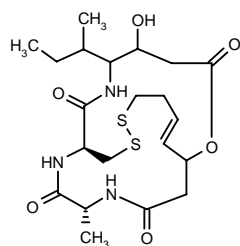
REFERENCES

1. Wang, S.-K. et al. *Cytotoxic constituents from leaves of Aglaia elliptifolia*. J Nat Prod 2001, 64(1): 92.

SPIRUCHOSTATIN B*

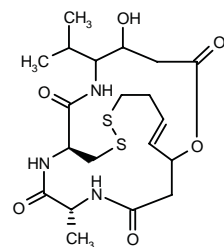
292763

(9*S*,20*R*)-5-Hydroxy-20-methyl-6-(1-methylpropyl)-2-oxa-11,12-dithia-7,19,22-triazabicyclo[7.7.6]docos-15-ene-3,8,18,21-tetrone



C21 H33 N3 O6 S2; Mol wt: 487.6387

ACTION – Potential antineoplastic agent with gene expression-enhancing activity, isolated from a *Pseudomonas* sp. In mink lung epithelial Mv1Lu cells, which express excess transforming growth factor β (TGF-β) receptors, resulting in expression of plasminogen activator inhibitor-1 (PAI-1), compound was found to mimic the effects of TGF-β and induce reporter gene expression under the control of the PAI-1 promoter; it also exerted potent cytostatic activity (IC₅₀ = 6.1 nM) but no cytotoxicity. Another depsipetide derived from the same source is:



Spiruchostatin A [292764]:** C20 H31 N3 O6 S2

SOURCE – Yamanouchi.

REFERENCES

1. Nagai, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel depsipeptide cpd*. WO 0042062.

2. Masuoka, Y. et al. *Spiruchostatins A and B, novel gene expression-enhancing substances produced by Pseudomonas sp.* Tetrahedron Lett 2001, 42(1): 41.

3. Masuoka, Y. et al. *Studies on spiruchostatin A and B, novel inducers of PAI-1 promoter expression*. Jpn J Cancer Res 2000, 91(Suppl.): Abst 2839.

*Identified compound **292763** Drug Data Rep 2001, 023(01): 0077.

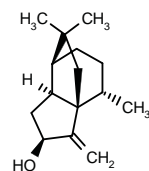
Identified compound **292764 (see **292763**) Drug Data Rep 2001, 023(01): 0077.

SUBEROLENOL A

300033

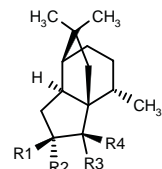
(2*S*,3*aS*,4*S*,7*S*,7*aS*)-4,8,8-Trimethyl-3-methylene-2,3,3*a*,4,5,6,7,7*a*-octahydro-3*a*,7-ethano-1*H*-inden-2-ol

(-)-Suberolenol A



C15 H24 O; Mol wt: 220.3536

ACTION – Cytotoxic agent isolated from the gorgonian *Isis hippuris*, proven to strongly inhibit the growth of human lung carcinoma A549 (ED₅₀ = 5100 μg/ml), murine leukemia P388 (ED₅₀ < 5.0 μg/ml) and human colon adenocarcinoma HT-29 cells (ED₅₀ < 5 μg/ml). A lead compound for further biological studies for the discovery of useful anticancer agents. Other suberosane sesquiterpenes from the same source are:



Compound	R1	R2	R3	R4	Formula
Suberosanone [300034]		-O-	H	Me	C ₁₅ H ₂₄ O
Suberolenol A acetate [300035]	OAc	H	-CH2-		C ₁₇ H ₂₆ O ₂
Suberolenol B acetate [300036]	H	OAc	-CH2-		C ₁₇ H ₂₆ O ₂

SOURCE – National Sun Yat-Sen University, Kaohsiung (TW).

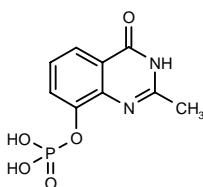
REFERENCES

1. Sheu, J.-H. et al. *New cytotoxic sesquiterpenes from the Gorgonian Isis hippuris*. J Nat Prod 2000, 63(12): 1603.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

297226

2-Methyl-4-oxo-3,4-dihydroquinazolin-8-yl dihydrogen phosphate



C9 H9 N2 O5 P; Mol wt: 256.1531

ACTION – A representative compound from a series of phosphate-type prodrugs of previously reported PARP (poly [ADP-ribose] polymerase, NAD⁺ ADP-ribosyl-transferase) inhibitors* with greatly improved water solubility compared to the parent compounds and which are readily converted to the parent drug *in vivo*.

SOURCE – University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

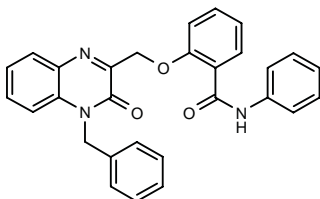
REFERENCES

1. Griffin, R.J. et al. (University of Newcastle upon Tyne) *Quinazolinone cpds*. US 6156739.

*See **NU-1025** Drug Data Rep 1996, 018(02): 0190.

299575

2-(4-Benzyl-3-oxo-3,4-dihydroquinoxalin-2-ylmethoxy)-*N*-phenylbenzamide



C29 H23 N3 O3; Mol wt: 461.5187

ACTION – Multidrug resistance modulator, a substituted quinoxaline that selectively antagonizes the P-glycoprotein (P-gp) transporter relative to multidrug resistance protein-1 (MRP-1) in drug-resistant breast cancer MCF-7 cell lines (selectivity index P-gp/MRP-1 = 13.4), being more potent and selective than verapamil; it exhibited low toxicity to sensitive MCF-7 cells (IC₅₀ > 54 μM).

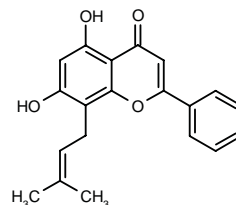
SOURCE – University of Pennsylvania, Philadelphia, PA (US).

REFERENCES

1. Lawrence, D.S. et al. *Structure-activity studies of substituted quinoxalinones as multiple-drug-resistance antagonists*. J Med Chem 2001, 44(4): 594.

300075

5,7-Dihydroxy-8-(3-methyl-2-butenyl)-2-phenyl-4*H*-1-benzopyran-4-one



C20 H18 O4; Mol wt: 322.3582

ACTION – Multidrug resistance modulator with high affinity for the P-glycoprotein (P-gp) cytosolic domain (K_d = 0.28 μM) and the ability to inhibit P-gp-mediated daunomycin efflux from leukemia K-562/R7 cells, leading to enhanced intracellular accumulation of the drug. Compound was not cytotoxic to cells at effective concentrations.

SOURCES – INSERM, Paris Cedex (FR); Université Claude Bernard Lyon 1, Villeurbanne Cedex (FR).

REFERENCES

1. Barron, D. and Mariotte, A.M. *Syntheses of 8-C-(1,1-dimethylallyl)flavones and 3-methyl flavonols*. Nat Prod Lett 1994, 4(1): 21.

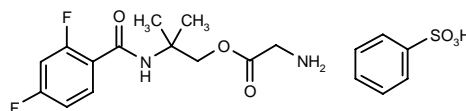
2. Comte, G. et al. *C-Isoprenylation of flavonoids enhances binding affinity toward P-glycoprotein and modulation of cancer cell chemoresistance*. J Med Chem 2001, 44(5): 763.

3. Conseil, G. et al. *Prenyl-flavonoids as potent inhibitors of the Pdr5p multidrug ABC transporter from Saccharomyces cerevisiae*. Biochemistry 2000, 39(23): 6910.

OCULAR MEDICATIONS

297584

Glycine 2-(2,4-difluorobenzamido)-2-methylpropyl ester benzenesulfonate



C13 H16 F2 N2 O3 . C6 H6 O3 S; Mol wt: 444.4528

SOURCE – National Sun Yat-Sen University, Kaohsiung (TW).

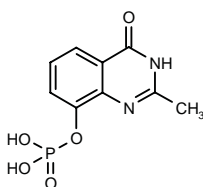
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1. Sheu, J.-H. et al. *New cytotoxic sesquiterpenes from the Gorgonian Isis hippuris*. J Nat Prod 2000, 63(12): 1603.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

297226

2-Methyl-4-oxo-3,4-dihydroquinazolin-8-yl dihydrogen phosphate



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SOURCE – University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

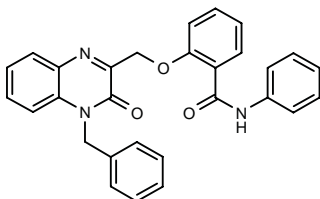
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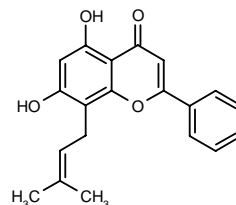
SOURCE – University of Pennsylvania, Philadelphia, PA (US).

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300075

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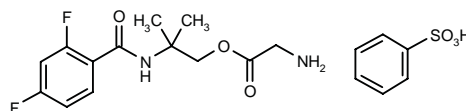
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3. Conseil, G. et al. *Prenyl-flavonoids as potent inhibitors of the Pdr5p multidrug ABC transporter from Saccharomyces cerevisiae*. Biochemistry 2000, 39(23): 6910.

OCULAR MEDICATIONS

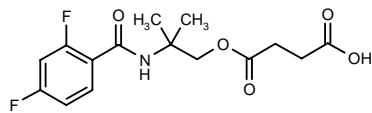
297584

Glycine 2-(2,4-difluorobenzamido)-2-methylpropyl ester benzenesulfonate



C13 H16 F2 N2 O3 . C6 H6 O3 S; Mol wt: 444.4528

ACTION – Agent for the treatment of nerve degeneration diseases including neuropil degenerative diseases that acts as a prodrug of a previously reported compound*. It was active in a rat model of retinal damage induced by white light when given at 100 mg/kg p.o. Another compound from this series of prodrugs of amide derivatives is:



297585: C15 H17 F2 N O5

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

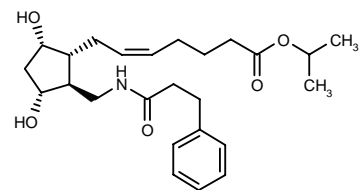
1. Nishihara, T. and Muraoka, M. (Sumitomo Pharmaceuticals Co., Ltd.) *Amide derivs.* WO 0064859.

*See **277508** (see **277506**) Drug Data Rep 1999, 021(09): 0836.

297371

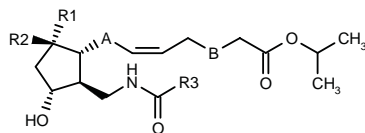
7-[(1*R*,2*S*,3*R*,5*S*)-3,5-Dihydroxy-2-(3-phenylpropionamidomethyl)cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

13-(3-Phenylpropionamido)-14,15,16,17,18,19,20-heptanorprostaglandin F_{2α} isopropyl ester



C25 H37 N O5; Mol wt: 431.5693

ACTION – Agent for the treatment of glaucoma and ocular hypertension, a representative compound from a series of 14-aza analogues of prostaglandins, particularly PGF_{2α}, PGD₂ and PGE₂, that are reported to exhibit an improved therapeutic profile when compared to natural (C-14) prostaglandins, as well as many of the known analogues. Other specifically claimed compounds are:



Compound	R1	R2	R3	A	B	Formula
297373	OH	H	3-Cl-PhOCH2	-CH2-	-CH2-	C ₂₄ H ₃₄ ClNO ₆
297374	OH	H	3-Cl-PhOCH2	-(CH2)2-	bond	C ₂₄ H ₃₄ ClNO ₆
297378	H	Cl	cyclohexyl	-CH2-	-O-	C ₂₂ H ₃₆ ClNO ₅

SOURCE – Alcon.

REFERENCES

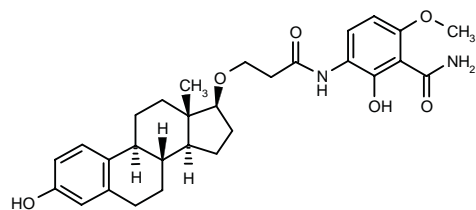
1. Selliah, R.D. (Alcon Laboratories, Inc.) *14-Aza prostaglandins for the treatment of glaucoma and ocular hypertension.* US 6160013.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

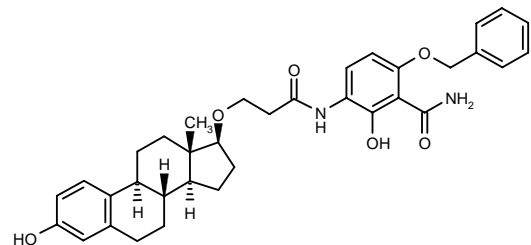
296648

2-Hydroxy-3-[3-[3-hydroxyestra-1,3,5(10)-trien-17β-yl]propionamido]-6-methoxybenzamide



C29 H36 N2 O6; Mol wt: 508.6114

ACTION – Agent for the treatment or prevention of degenerative bone disorders, a representative compound from a series of derivatives comprising a first moiety having affinity for the extracellular inorganic matrix of bone and a second moiety having bone formation-increasing activity and/or bone resorption-inhibitory activity such as a sex hormone. *In vitro*, compound was shown to exhibit strong bone-targeting activity, as measured by its ability to bind to microcrystalline hydroxyapatite in an aqueous solution, being more potent than tetracycline, which is known to have strong binding affinity for bone. When tested *in vivo* in ovariectomized rats, compound exhibited bone-preserving activity (ED₅₀ = 361 nmol/kg p.o.), while exhibiting minimal estrogenic activity in the uterus. Another exemplified compound is:



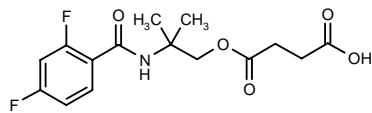
296650: C35 H40 N2 O6

SOURCE – Research Corporation Technologies.

REFERENCES

1. Pierce, W.M. Jr. et al. (Research Corporation Technologies, Inc.) *Bone targeting agents for osteoporosis.* WO 0066613.

ACTION – Agent for the treatment of nerve degeneration diseases including neuropil degenerative diseases that acts as a prodrug of a previously reported compound*. It was active in a rat model of retinal damage induced by white light when given at 100 mg/kg p.o. Another compound from this series of prodrugs of amide derivatives is:



297585: C15 H17 F2 N O5

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

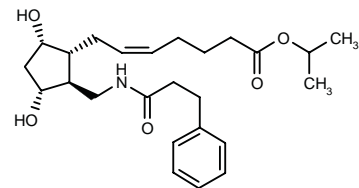
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*See **277508** (see **277506**) Drug Data Rep 1999, 021(09): 0836.

297371

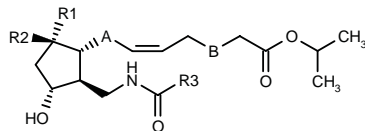
7-[(1*R*,2*S*,3*R*,5*S*)-3,5-Dihydroxy-2-(3-phenylpropionamidomethyl)cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

13-(3-Phenylpropionamido)-14,15,16,17,18,19,20-heptanorprostaglandin F_{2α} isopropyl ester



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Compound	R1	R2	R3	A	B	Formula
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297374	OH	H	3-Cl-PhOCH2	-(CH2)2-	bond	C ₂₄ H ₃₄ ClNO ₆
297378	H	Cl	cyclohexyl	-CH2-	-O-	C ₂₂ H ₃₆ ClNO ₅

SOURCE – Alcon.

REFERENCES

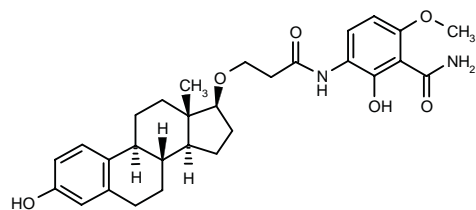
1. Selliah, R.D. (Alcon Laboratories, Inc.) *14-Aza prostaglandins for the treatment of glaucoma and ocular hypertension.* US 6160013.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

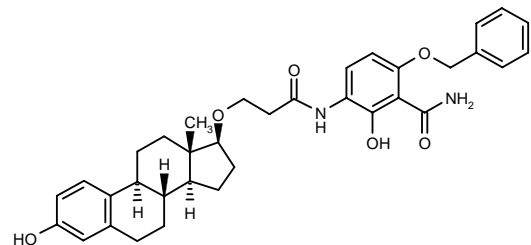
296648

2-Hydroxy-3-[3-[3-hydroxyestra-1,3,5(10)-trien-17β-yl]propionamido]-6-methoxybenzamide



C29 H36 N2 O6; Mol wt: 508.6114

ACTION – Agent for the treatment or prevention of degenerative bone disorders, a representative compound from a series of derivatives comprising a first moiety having affinity for the extracellular inorganic matrix of bone and a second moiety having bone formation-increasing activity and/or bone resorption-inhibitory activity such as a sex hormone. *In vitro*, compound was shown to exhibit strong bone-targeting activity, as measured by its ability to bind to microcrystalline hydroxyapatite in an aqueous solution, being more potent than tetracycline, which is known to have strong binding affinity for bone. When tested *in vivo* in ovariectomized rats, compound exhibited bone-preserving activity (ED₅₀ = 361 nmol/kg p.o.), while exhibiting minimal estrogenic activity in the uterus. Another exemplified compound is:



296650: C35 H40 N2 O6

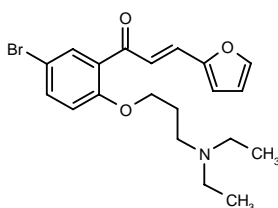
SOURCE – Research Corporation Technologies.

REFERENCES

1. Pierce, W.M. Jr. et al. (Research Corporation Technologies, Inc.) *Bone targeting agents for osteoporosis.* WO 0066613.

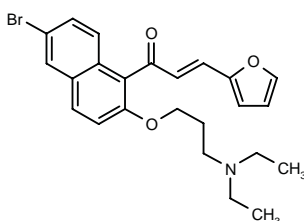
297218

1-[5-Bromo-2-[3-(diethylamino)propoxy]phenyl]-3-(2-furanyl)-2(*E*)-propen-1-one



C20 H24 Br N O3; Mol wt: 406.3176

ACTION – Agent for the treatment of inflammation and osteoporosis proven to prevent bone destruction in ovariectomized rats. LD₅₀ > 100 mg/kg i.p. in mice. Another compound from this series of alkylamine derivatives is:



297220: C24 H26 Br N O3

SOURCE – Kaken.

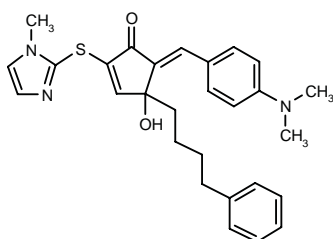
REFERENCES

1. Ohara, T. et al. (Kaken Pharmaceutical Co., Ltd.) *Alkylamine derivs.* JP 2000256286.

TEI-6363

299721

5-[(*E*)-4-(Dimethylamino)benzylidene]-4-hydroxy-2-(1-methyl-1*H*-imidazol-2-ylsulfanyl)-4-(4-phenylbutyl)-2-cyclopenten-1-one



C28 H31 N3 O2 S; Mol wt: 473.6379

ACTION – Prostaglandin A₁ derivative proven to induce osteoblastic differentiation of rat osteosarcoma-derived ROA17/2.8 cells via suppression of cell growth and induction of cell cycle arrest at the G1 phase, as well as activation of alkaline phosphatase and increase in collagen synthesis. These effects appeared to be independent of a cytotoxic effect.

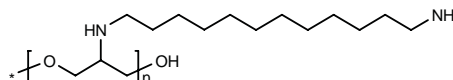
SOURCE – Teijin.

REFERENCES

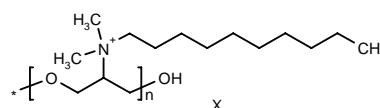
1. Miura, D. et al. *Effect of the novel prostaglandin A₁ derivative TEI-6363 on ROS17/2.8 cell differentiation in vitro.* Jpn J Pharmacol 2000, 83(3): 246.

TREATMENT OF LIPOPROTEIN DISORDERS

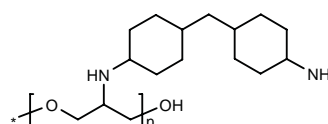
296673



ACTION – Bile acid sequestrant, as demonstrated in hamsters, where it induced high bile acid excretion into feces following administration in the diet at 0.20%, being more potent than colestevlam, colestipol and cholestyramine. Potentially useful for reducing cholesterol and for the treatment of atherosclerosis and hypercholesterolemia. Other exemplified polyether-based polymers include the following:



Compound	X
296676	Cl ⁻
296677	O ⁻



296795

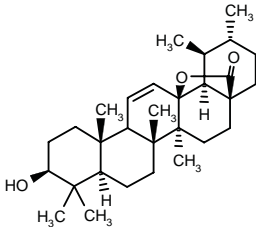
SOURCE – GelTex (Genzyme General).

REFERENCES

1. Holmes-Farley, S.R. and Huval, C.C. (GelTex Pharmaceuticals, Inc.) *Polyether-based bile acid sequestrants.* WO 0064428.

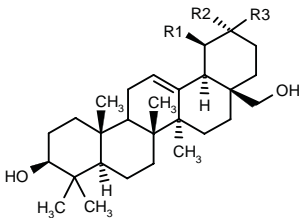
296909

(1*S*,2*R*,4*aR*,6*aS*,6*bR*,8*aR*,10*S*,12*aS*,14*aR*)-10-Hydroxy-1,2,6*a*,6*b*,9,9,12*a*-heptamethyl-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,12*b*,14*a*,14*b*-icosahydro-14*b*,4*a*-(epoxymethano)picen-16-one

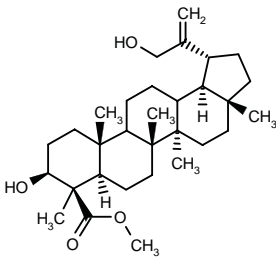


C30 H46 O3; Mol wt: 454.6904

ACTION – An inhibitor of ACAT, as demonstrated by 116.6% inhibition of ACAT from rat hepatic microsomes at 0.05 mg/ml. Potentially useful for the treatment of arteriosclerosis. Other exemplified compounds from this series of triterpene derivatives include the following:



Compound	R1	R2	R3	Formula
296910	H	Me	Me	C ₃₀ H ₅₀ O ₂
296911	Me	Me	H	C ₃₀ H ₅₀ O ₂



296912: C31 H50 O4

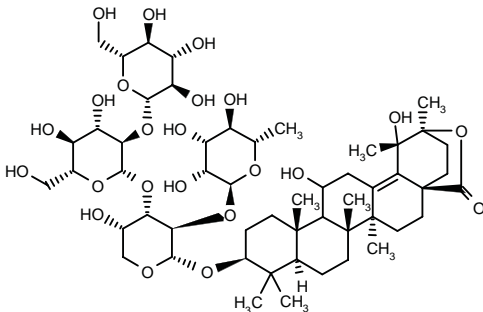
SOURCE – Pola Chemical.

REFERENCES

1. Nishimura, K. et al. (Pola Chemical Industries Inc.) *Triterpene and ACAT inhibitors containing it*. JP 2000256392.

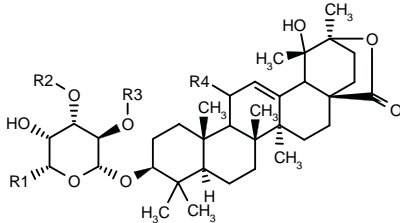
296914

(1*S*,2*S*,4*aR*,6*aS*,6*bR*,8*aS*,10*S*,12*aS*)-1,13-Dihydroxy-1,2,6*a*,6*b*,9,9,12*a*-heptamethyl-15-oxo-2,4*a*-(epoxymethano)-1,2,3,4*a*,5,6,6*a*,7,8,9,10,11,12,12*a*,12*b*,13,14-icosahydricen-10-yl 2-*O*-(6-deoxy- α -L-mannopyranosyl)-3-*O*-[2-*O*-(β -D-glucopyranosyl)- β -D-glucopyranosyl]- α -L-arabinopyranoside

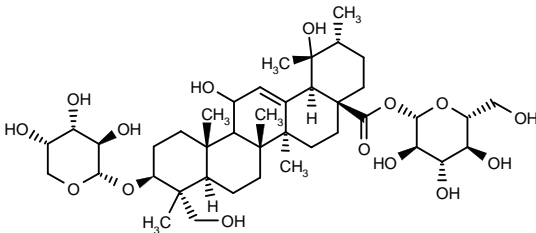


C53 H84 O23; Mol wt: 1089.2240

ACTION – An inhibitor of ACAT, as demonstrated by 110.5% inhibition of ACAT from rat hepatic microsomes at 0.05 mg/ml. Potentially useful for the treatment of arteriosclerosis. Other exemplified compounds from this series of saponin derivatives include the following:



Compound	R1	R2	R3	R4	Formula
296915	CH2-OH	H	β -D-glucopyranosyl	OH	C ₄₂ H ₆₆ O ₁₅
296917	H	2- <i>O</i> -(β -D-glucopyranosyl)- β -D-glucopyranosyl	6-deoxy- α -L-mannopyranosyl	H	C ₅₃ H ₈₄ O ₂₂



296916: C41 H66 O15

SOURCE – Pola Chemical.

REFERENCES

1. Nishimura, K. et al. (Pola Chemical Industries Inc.) *Saponin and ACAT inhibitors containing them*. JP 2000256391.

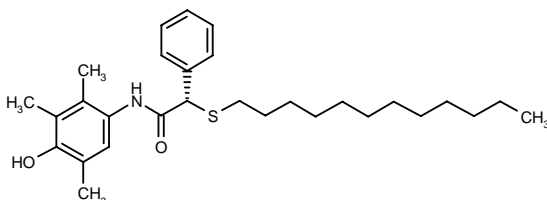
EFLUCIMIBE*

Prop INN

253368

2-(S)-(Dodecylsulfanyl)-N-(4-hydroxy-2,3,5-trimethylphenyl)-2-phenylacetamide

F-12511



C29 H43 N O2 S; Mol wt: 469.7297

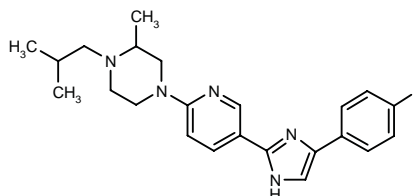
ACTION – Potent ACAT inhibitor (IC_{50} = 3, 7 and 71 nM, respectively, against human enzyme in HepG2, CaCo-2 and THP-1 cells) with comparable activity to CP-113818 (IC_{50} = 6, 9 and 63 nM, respectively). *In vivo*, compound exerted cholesterol-lowering activity in cholesterol-fed rats (ED_{50} = 0.12 mg/kg) and guinea pigs (ED_{30} = 0.008 mg/kg) after oral administration. In New Zealand cholesterol-fed rabbits, compound not only prevented the increase in plasma total cholesterol (ED_{50} = 0.37 mg/kg p.o.), but also reduced the incidence of aortic fatty streaks and prevented the impairment of endothelial function at the dose of 2.5 mg/kg. In chow-fed hamsters, compound induced a dose-dependent reduction in plasma cholesterol (maximal reduction of 31% at 40 mg/kg/day for 10 days) and preferentially decreased VLDL (47%) and LDL (29%), although it also reduced HDL at this dose (27%). In this model, compound also dose-dependently decreased hepatic cholesteryl ester levels (ED_{50} = 1.40 mg/kg), reduced free cholesterol by 33% at 40 mg/kg and decreased liver ACAT activity by 30%. No impairment of adrenal function was seen in guinea pigs at up to 2.5 mg/kg by gavage, a dose higher than its ED_{30} for reducing plasma cholesterol levels. Currently undergoing phase I clinical trials for the treatment of atherosclerosis.

SOURCES – Lilly; Pierre Fabre (bioMerieux-Pierre Fabre).**REFERENCES**

1. Patoiseau, J.-F. et al. (Pierre Fabre Médicament) *Novel 2,3,5-trimethyl-4-hydroxy anilide derivs., preparation thereof*. EP 0874812, FR 2741619, JP 2000500771, US 5990173, WO 9719918.
2. Delhon, A. et al. *F 12511 exerts hypolipidemic effects in normocholesterolemic hamsters through hepatic ACAT inhibition*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 48.
3. Junquero, D. et al. *F 12511, a novel ACAT inhibitor, and atorvastatin regulate endogenous hypercholesterolemia in a synergistic manner in New Zealand rabbits fed a casein-enriched diet*. Atherosclerosis 2001, 155(1): 131.
4. Junquéro, D. et al. *F 12511: A potent inhibitor of cholesterol esterification in cultured cells*. 11th Int Symp Atheroscler (Oct 5-9, Paris) 1997, Abst Book Suppl., Abst 385.
5. Junquero, D. et al. *Lack of toxic effects of F 12511, a novel potent inhibitor of acylcoenzyme A:cholesterol O-acyltransferase, on human adrenocortical cells in culture*. Biochem Pharmacol 2001, 61(4): 387.
6. Junquéro, D. et al. *Lipid regulating properties of the novel ACAT inhibitor F 12511 in rabbits fed a cholesterol-free casein-rich diet*. 11th Int Symp Atheroscler (Oct 5-9, Paris) 1997, Abst Book Suppl., Abst 386.
7. Junquero, D. et al. *Pharmacological profile of F 12511, (S)-2',3',5'-trimethyl-4'-hydroxy- α -dodecylthioacetanilide a powerful and systemic acylcoenzyme A:cholesterol acyltransferase inhibitor*. Biochem Pharmacol 2001, 61(1): 97.
8. *Pierre Fabre strengthens R&D programs; company pipeline in review*. DailyDrugNews.com (Daily Essentials) 1999, May 28.

*Identified compound **253368** (see **252989**) Drug Data Rep 1997, 019(09): 0848.**TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS****296715**

4-[5-[4-(4-Fluorophenyl)-1H-imidazol-2-yl]pyridin-2-yl]-1-isobutyl-2-methylpiperazine



C23 H28 F N5; Mol wt: 393.5072

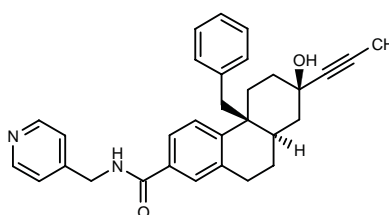
ACTION – Agent for the treatment of obesity, a neuropeptide Y (NPY) Y_5 receptor antagonist. A representative compound from a series of substituted imidazole derivatives.

SOURCE – Pfizer.**REFERENCES**

1. Elliott, R.L. et al. (Pfizer Products Inc.) *Cpds. for the treatment of obesity*. WO 0066578.

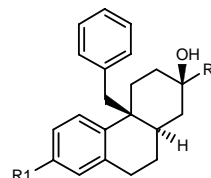
296893

(4bS,7R,8aR)-4b-Benzyl-7-hydroxy-7-(1-propynyl)-N-(4-pyridinylmethyl)-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-2-carboxamide



C31 H32 N2 O2; Mol wt: 464.6058

ACTION – Nonsteroidal compound that acts as a selective glucocorticoid receptor modulator and is specifically claimed for the treatment of obesity, diabetes, anxiety, depression, neurodegeneration or antiinflammatory diseases. Other exemplified compounds are:



Compound	R1	R2	Formula
296894	OCONHCH2CH2N(Me)2	1-propynyl	C ₂₉ H ₃₆ N ₂ O ₃
296895	2-Pyr-CH2O	1-propynyl	C ₃₀ H ₃₁ NO ₂
296896	2-Me-3-Pyr-CH2NHCO	Pr	C ₃₂ H ₃₈ N ₂ O ₂
296897	2-Me-3-Pyr-CH2O	CH2CH2CF3	C ₃₁ H ₃₄ F ₃ NO ₂
296898	3-Pyr-NHCO	Me	C ₂₈ H ₃₀ N ₂ O ₂

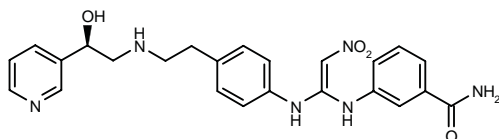
SOURCE – Pfizer.

REFERENCES

1. Dow, R.L. et al. (Pfizer Products Inc.) *Glucocorticoid receptor modulators*. WO 0066522.

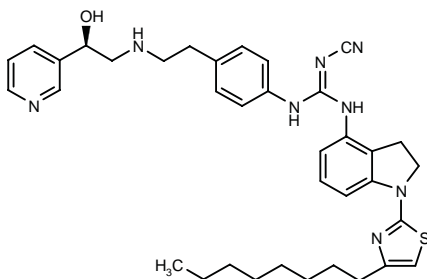
299800

3-[1-[4-[2-[2(*R*)-Hydroxy-2-(3-pyridyl)ethylamino]-ethyl]phenylamino]-2(*Z*)-nitroethenylamino]benzamide

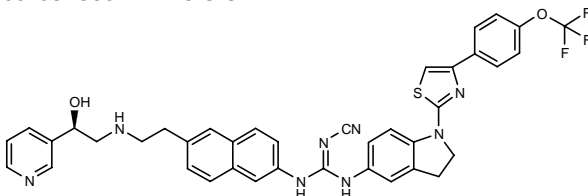


C24 H26 N6 O4; Mol wt: 462.5074

ACTION – Human β_3 -adrenoceptor full agonist (EC_{50} = 10 nM for adenylyl cyclase activation in CHO cells expressing the human receptor) with over 70-fold selectivity over β_1 - and β_2 -adrenoceptors (IC_{50} = 790 and 1200 nM, respectively, in binding assays). Potentially useful for the treatment of obesity. Other related compounds are:



299798: C36 H44 N8 O S



299799: C39 H33 F3 N8 O2 S

SOURCE – Merck & Co.

REFERENCES

1. Brockunier, L.L. et al. *Human β_3 adrenergic receptor agonists containing cyanoguanidine and nitroethylenediamide moieties*. Bioorg Med Chem Lett 2001, 11(3): 379.

AOD-9604

271145

L-Tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutamyl-L-cysteinyl-L-arginyl-L-seryl-L-valyl-L-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-L-phenylalanyl cyclic (7-14)-disulfide

C78 H123 N23 O23 S2; Mol wt: 1815.1000

ACTION – Synthetic analogue of the lipolytic domain of human growth hormone (hGH), able to significantly reduce body weight gain by 50% (compared to control animals) in obese Zucker rats when given at a daily dose of 500 μ g/kg p.o. for 19 days; this effect appeared to be at least partially attributable to an increase in lipolytic activity of adipose tissue. In contrast to hGH, chronic treatment with AOD-9604 was not associated with reduced insulin sensitivity, and preliminary toxicity experiments indicated no hematological, biochemical or other abnormalities after chronic treatment with compound. Potentially useful for the treatment of obesity.

SOURCES – Metabolic Pharmaceuticals; Monash University, Clayton (AU).

REFERENCES

1. Ng, F.M.-W. and Jiang, W.-J. (Metabolic Pharmaceuticals, Ltd.) *Treatment of obesity*. WO 9912969.

2. Heffernan, M.A. et al. *The effect of a modified C-terminal fragment of human growth hormone on β -adrenoceptor expression and function in human SK-N-MC neuroblastoma cells*. Mol Control Adipogenesis Obes (Feb 16-22, Taos) 2000, Abstr 409.

3. Ng, F.M. et al. *Metabolic studies of a synthetic lipolytic domain (AOD9604) of human growth hormone*. Horm Res 2000, 53(6): 274.

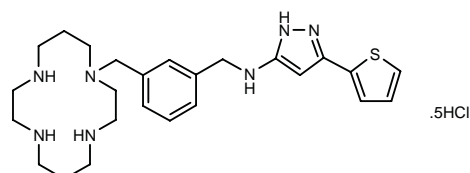
4. *Company Profile: Metabolic Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) 1999, Jan 4.

5. *Progress report on Metabolic's obesity and diabetes programs*. DailyDrugNews.com (Daily Essentials) 2001, Jan 12.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

296635

N-[3-(1,4,8,11-Tetraazacyclotetradecan-1-ylmethyl)-benzyl]-N-[3-(2-thienyl)-1H-pyrazol-5-yl]amine pentahydrochloride



C25 H37 N7 S . 5HCl; Mol wt: 649.9868

ACTION – CXCR4 receptor antagonist for use as a thrombopoietin (TPO) mimetic in promoting thrombopoiesis and megakaryocytopoiesis in the treatment of thrombocytopenia and other conditions with depressed platelet production. When tested in a luciferase assay in TPO-responsive murine BaF3 cells, compound produced 86% of maximal TPO effect, with an EC_{50} value of 2.7 μ M. A representative compound from a series of substituted cyclam derivatives.

SOURCE – GlaxoSmithKline.

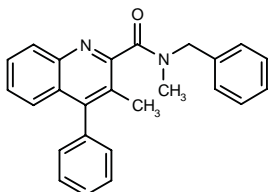
REFERENCES

1. Luengo, J.I. et al. (SmithKline Beecham Corp.) *CXCR-4 receptor antagonists - Thrombopoietin mimetics*. WO 0066112.

DIAGNOSTIC AGENTS

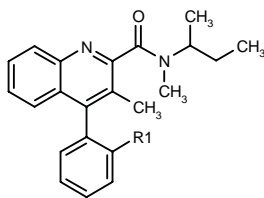
299579

N-Benzyl-*N*,3-dimethyl-4-phenylquinoline-2-carboxamide



C₂₅ H₂₂ N₂ O; Mol wt: 366.4618

ACTION – Selective ligand for the peripheral benzodiazepine receptor (PBR) binding site ($IC_{50} = 2.1$ nM), with high *in vivo* specific binding to PBR in heart, lung, kidney, adrenal gland, spleen and brain when given to rats as the [¹¹C]-radiolabeled form. Suitable for use as a radioligand for quantification and visualization of PBR with positron emission tomography. Other potential radioligands are:



Compound	R1	Formula
299580	H	C ₂₂ H ₂₄ N ₂ O
299581	F	C ₂₂ H ₂₃ FN ₂ O

SOURCES – Università degli Studi di Catanzaro, Catanzaro (IT); Università degli Studi di Milano, Milano (IT); Università degli Studi di Siena, Siena (IT).

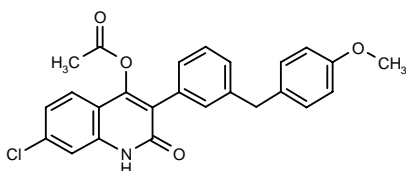
REFERENCES

1. Cappelli, A. et al. Mapping the peripheral benzodiazepine receptor binding site by conformationally restrained derivatives of 1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methyl-propyl)-3-isoquinolinecarboxamide (PK11195). *J Med Chem* 1997, 40(18): 2910.

2. Matarrese, M. et al. Labeling and evaluation of *N*-[¹¹C]methylated quinolone-2-carboxamides as potential radioligands for visualization of peripheral benzodiazepine receptors. *J Med Chem* 2001, 44(4): 579.

299593

Acetic acid 7-chloro-3-[3-(4-methoxybenzyl)phenyl]-2-oxo-1,2-dihydroquinolin-4-yl ester



C₂₅ H₂₀ Cl N O₄; Mol wt: 433.8890

ACTION – Prodrug of L-703717*, a high-affinity antagonist at the glycine site of the NMDA receptor, with improved blood–brain barrier permeability compared to the active compound. Studies on brain penetration employing the [¹¹C]-labeled analogue of the prodrug demonstrated an improved uptake in both brain and cerebellum compared with [¹¹C]-L-703717 in mice, rats and monkeys. Metabolism studies in rat brain homogenates indicated that [¹¹C]-prodrug is rapidly converted to the active compound, giving 80% bioconversion after 20-min incubation. Potentially useful as a radioligand to study the physiological and pathological roles of the cerebellar glycine site in living brain in conjunction with positron emission tomography (PET).

SOURCES – Japan Science and Technology; Kyushu University, Fukuoka-shi (JP); National Institute of Radiological Sciences, Chiba (JP).

REFERENCES

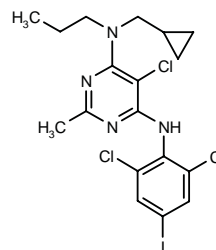
1. Haradahira, T. et al. (Japan Science and Technology Corp.; National Institute of Radiological Sciences) ¹¹C-Labeled cpds. and measurement method of intracerebral NMDA receptor. *JP* 2001011052.

2. Haradahira, T. et al. A prodrug of NMDA/glycine site antagonist, L-703717, with improved BBB permeability: 4-Acetoxy derivative and its positron-emitter labeled analog. *Chem Pharm Bull* 2001, 49(2): 147.

*See L-701324 Drug Data Rep 1995, 017(01): 0035.

299790

5-Chloro-*N*⁴-(cyclopropylmethyl)-*N*⁶-(2,6-dichloro-4-iodophenyl)-2-methyl-*N*⁴-propylpyrimidine-4,6-diamine



C₁₈ H₂₀ Cl₃ I N₄; Mol wt: 525.6430

ACTION – The first nonpeptide, high-affinity ligand for corticotropin-releasing factor receptor CRF₁ ($K_i = 14$ nM), a potential candidate for single photon emission computed tomography (SPECT) imaging and as a selective radioligand for this receptor in binding assays.

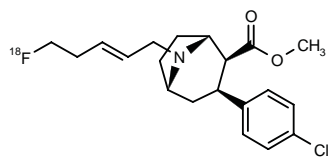
SOURCES – National Institute on Drug Abuse, Bethesda, MD (US); National Institutes of Health, Bethesda, MD (US).

REFERENCES

1. Tian, X. et al. The development of a potential single photon emission computed tomography (SPECT) imaging agent for the corticotropin-releasing hormone receptor type 1. *Bioorg Med Chem Lett* 2001, 11(3): 331.

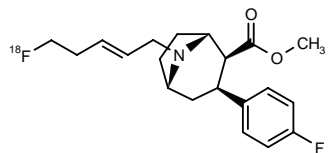
296621

3*exo*-(4-Chlorophenyl)-8-[5-¹⁸F]fluoro-2(*E*)-pentenyl]-8-azabicyclo[3.2.1]octane-2*exo*-carboxylic acid methyl ester



C20 H25 Cl F N O2; Mol wt: 364.8755

ACTION – Agent that binds to the dopamine transporter (DAT) with high affinity and selectivity, useful as an imaging agent for visualizing the location and density of DAT, for example in Parkinson’s patients, by positron emission tomography (PET). Compound was found to be stable to metabolism and *in vivo* loss of the ¹⁸F radioisotope. In binding assays, the unlabeled parent compound had a K_i value of 2.4 nM against [³H]-Win-35428 binding in cells stably transfected with human DAT, while exhibiting respective K_i values of > 10,000 nM and 12.1 nM for the norepinephrine and 5-HT transporters. Following injection to rats, compound showed good striatum (S) uptake (2.5% dose/g at 120 min) with rapid clearance from the cerebellum (CB) and cortex (CX), giving S/CB and S/CX ratios of 15 and 7, respectively, at 120 min postinjection. Brain PET imaging in rhesus monkeys revealed high S uptake and rapid CB and CX washout resulting in S/CB and S/CX of 12.9 and 11.4, respectively, at 180-210 min. Another compound from this series of fluoroalkenylnortropans is:



296627: C20 H25 F2 N O2

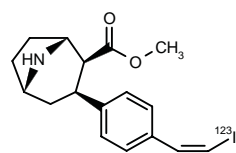
SOURCE – Emory University, Atlanta, GA (US).

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1. Goodman, M.M. and Chen, P. (Emory University) *Fluoroalkenyl nortropans*. WO 0064490.

296631

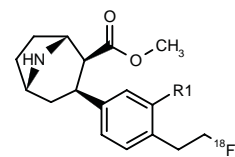
3*exo*-[4-[(*Z*)-2-[¹²³I]iodovinyl]phenyl]-8-azabicyclo[3.2.1]octane-2*exo*-carboxylic acid methyl ester



C17 H20 I N O2; Mol wt: 393.3500

ACTION – Agent that binds to the 5-HT transporter (SERT) with high affinity and selectivity, useful as an imaging agent for visualizing the location and density of SERT, for example in the brain of patients suffering from major depression, obsessive–compulsive disorder or cocaine addiction, by single photon emission computed tomography (SPECT). Compound was found to be stable

to metabolism and *in vivo* loss of the ¹²³I isotope. In binding assays, the unlabeled parent compound had a K_i value of 0.031 nM against [³H]-citalopram binding in cells stably transfected with human SERT, while exhibiting K_i values of 3.47 nM and 15 nM for the dopamine and norepinephrine trans-porters, respectively. Following injection to rats, com-pound showed high accumulation in brain regions rich in serotonergic neurons, with hypo-thalamus/cerebellum ratios of 3:1 and 5:1 at 60 and 120 min postinjection, respectively, and a prefrontal cortex/cerebellum ratios of 2.9 : 1 at 120 min postinjection. Brain SPECT imaging in rhesus monkeys revealed high uptake in the midbrain by 54 min postinjection. Other compounds from this series of 4-fluoroalkyl-3-halo-phenylnortropans include the following:



Compound	R1	Formula
296632	Br	C ₁₇ H ₂₁ BrFNO ₂
296633	I	C ₁₇ H ₂₁ FINO ₂

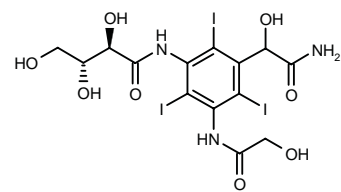
SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

1. Goodman, M.M. and Chen, P. (Emory University) *4-Fluoroalkyl-3-halophenyl nortropans*. WO 0064491.

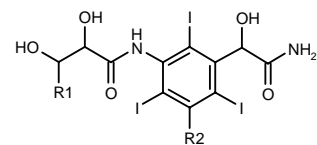
296827

N-[3-(2-Amino-1-hydroxy-2-oxoethyl)-5-(2-hydroxy-acetamido)-2,4,6-triiodophenyl]-2(*R*),3(*R*),4-trihydroxy-butyramide



C14 H16 I3 N3 O8; Mol wt: 734.9934

ACTION – Iodinated compound useful as an X-ray contrast agent that exhibits low viscosity and high hydrophilicity. It has a viscosity of 8.8 mPas in aqueous solution at 20 °C and a concentration of 350 mg iodide/ml. Other specifically claimed iodinated aryl compounds are:



Compound	R1	R2	Isomer	Formula
296828	CH2OH	NHCOCH2OH	2(R),3(S)	C ₁₄ H ₁₆ I ₃ N ₃ O ₈
296829	H	CONHCH2CH(OH)CH2OH		C ₁₅ H ₁₈ I ₃ N ₃ O ₈

SOURCE – Nycomed Imaging.

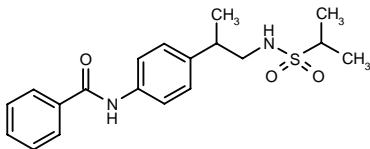
REFERENCES

1. Rebecca, G. et al. (Nycomed Imaging AS) *Contrast media*. WO 0066544.

PHARMACOLOGICAL TOOLS

298907

N-[4-[2-(Isopropylsulfonamido)-1-methylethyl]phenyl]-benzamide



C19 H24 N2 O3 S; Mol wt: 360.4756

ACTION – AMPA receptor potentiator proven to increase AMPA receptor-mediated inward currents in cerebellar Purkinje neurons. Experiments with tritiated compound demonstrated that it is the first compound reported to label with nanomolar affinity a putative AMPA receptor potentiator site on heteromeric AMPA receptors in rat cortical membranes. Potentially useful as a pharmacological tool to elucidate the pharmacology of AMPA receptors and as a prototype for use in developing treatments for neuropsychiatric disorders such as age-associated memory impairment and schizophrenia.

SOURCE – Lilly.

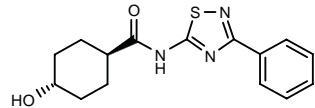
REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) *N-Substd. sulfonamide derivs*. WO 0006537.
2. Arnold, M.B. et al. (Eli Lilly and Company) *Sulphonamide derivs*. EP 0860428, WO 9833496.
3. Zarrinmayed, H. et al. *[3H]N-2-(4-Benzamido)phenyl)propyl-2-propanesulfonamide: A novel AMPA receptor potentiator and radioligand*. J Med Chem 2001, 44(3): 302.

VUF-5472

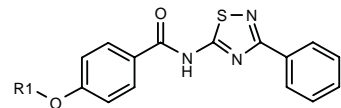
298613

trans-4-Hydroxy-*N*-(3-phenyl-1,2,4-thiadiazol-5-yl)cyclohexanecarboxamide



C15 H17 N3 O2 S; Mol wt: 303.3843

ACTION – Potent and selective adenosine A₁ receptor antagonist with high binding affinity for rat A₁ receptors (K_i = 0.020 μM) versus rat A_{2A} (K_i > 10 μM) and human A₃ receptors (K_i = 1.9 μM). Potentially useful as a tool for the elucidation of structural requirements for molecular recognition at adenosine receptors. Other thiadiazole analogues are:



Compound	R1	Formula
LUF-5437 [298611]	H	C ₁₅ H ₁₁ N ₃ O ₂ S
LUF-5417 [298612]	Me	C ₁₆ H ₁₃ N ₃ O ₂ S

SOURCES – Universiteit Leiden, Leiden (NL); Vrije Universiteit, Amsterdam (NL).

REFERENCES

1. van Muijlwijk, J.E. et al. *Thiazole and thiadiazole analogues as a novel class of adenosine receptor antagonists*. J Med Chem 2001, 44(5): 749.

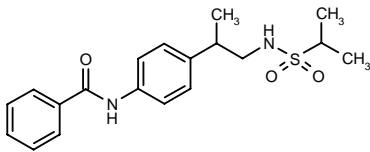
REFERENCES

1. Rebecca, G. et al. (Nycomed Imaging AS) *Contrast media*. WO 0066544.

PHARMACOLOGICAL TOOLS

298907

N-[4-[2-(Isopropylsulfonamido)-1-methylethyl]phenyl]-benzamide



C19 H24 N2 O3 S; Mol wt: 360.4756

ACTION – AMPA receptor potentiator proven to increase AMPA receptor-mediated inward currents in cerebellar Purkinje neurons. Experiments with tritiated compound demonstrated that it is the first compound reported to label with nanomolar affinity a putative AMPA receptor potentiator site on heteromeric AMPA receptors in rat cortical membranes. Potentially useful as a pharmacological tool to elucidate the pharmacology of AMPA receptors and as a prototype for use in developing treatments for neuropsychiatric disorders such as age-associated memory impairment and schizophrenia.

SOURCE – Lilly.

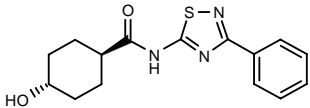
REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) *N-Substd. sulfonamide derivs*. WO 0006537.
2. Arnold, M.B. et al. (Eli Lilly and Company) *Sulphonamide derivs*. EP 0860428, WO 9833496.
3. Zarrinmayed, H. et al. *[3H]N-2-(4-Benzamido)phenyl)propyl-2-propanesulfonamide: A novel AMPA receptor potentiator and radioligand*. J Med Chem 2001, 44(3): 302.

VUF-5472

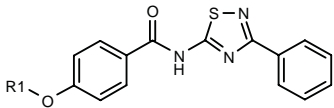
298613

trans-4-Hydroxy-*N*-(3-phenyl-1,2,4-thiadiazol-5-yl)cyclohexanecarboxamide



C15 H17 N3 O2 S; Mol wt: 303.3843

ACTION – Potent and selective adenosine A₁ receptor antagonist with high binding affinity for rat A₁ receptors (K_i = 0.020 μM) versus rat A_{2A} (K_i > 10 μM) and human A₃ receptors (K_i = 1.9 μM). Potentially useful as a tool for the elucidation of structural requirements for molecular recognition at adenosine receptors. Other thiadiazole analogues are:



Compound	R1	Formula
LUF-5437 [298611]	H	C ₁₅ H ₁₁ N ₃ O ₂ S
LUF-5417 [298612]	Me	C ₁₆ H ₁₃ N ₃ O ₂ S

SOURCES – Universiteit Leiden, Leiden (NL); Vrije Universiteit, Amsterdam (NL).

REFERENCES

1. van Muijlwijk, J.E. et al. *Thiazole and thiadiazole analogues as a novel class of adenosine receptor antagonists*. J Med Chem 2001, 44(5): 749.

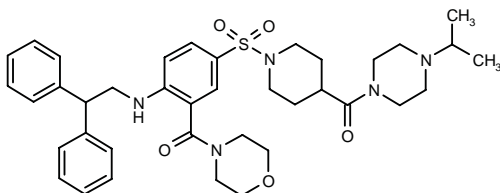
ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

298736

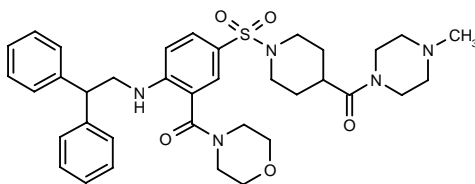
N-(2,2-Diphenylethyl)-4-[4-(4-isopropylpiperazin-1-ylcarbonyl)piperidin-1-ylsulfonyl]-2-(4-morpholinylcarbonyl)-aniline

1-[1-[4-(2,2-Diphenylethylamino)-3-(4-morpholinylcarbonyl)phenylsulfonyl]piperidin-4-yl]-1-(4-isopropylpiperidin-1-yl)methanone



C38 H49 N5 O5 S; Mol wt: 687.9011

ACTION – Bradykinin receptor antagonist, potentially useful for the treatment or prevention of pain and inflammatory diseases, especially inflammatory pain. Another specifically claimed compound is:



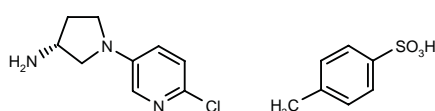
298737: C36 H45 N5 O5 S

SOURCE – Novartis.

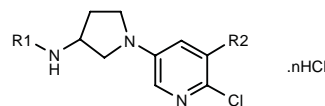
REFERENCES

1. Brain, C.T. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Bradykinin receptor antagonists*. WO 0075107.

297975

1-(6-Chloropyridin-3-yl)pyrrolidin-3(*R*)-amine 4-methylbenzenesulfonateC₉ H₁₂ Cl N₃ . C₇ H₈ O₃ S; Mol wt: 369.8710

ACTION – Selective neurotransmitter release-controlling agent that was found to bind to the nicotinic acetylcholine receptor ($K_i = 0.22 \text{ nM}$) and demonstrated analgesic activity in the mouse hot-plate assay ($\text{MED} = 1.9 \mu\text{mol/kg i.p.}$). This compound is indicated for the treatment of pain, Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder, depression, nicotine withdrawal syndrome, Tourette's syndrome and schizophrenia. Other exemplified heterocyclic substituted aminoazacyclic compounds are:



Compound	R1	R2	Isomer	n	Formula
297976	H	Me	R	1	C ₁₀ H ₁₅ Cl ₂ N ₃
297977	H	Me	S	2	C ₁₀ H ₁₆ Cl ₃ N ₃
297978	H	Cl	S	2	C ₉ H ₁₃ Cl ₄ N ₃
297979	Me	Me	R	2	C ₁₁ H ₁₆ Cl ₃ N ₃

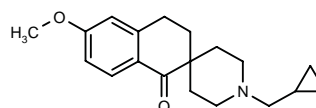
SOURCE – Abbott.

REFERENCES

1. Schrimpf, M.R. et al. (Abbott Laboratories Inc.) *Heterocyclic substd. aminoazacycles useful as central nervous system agents*. WO 0071534.

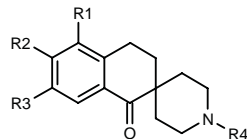
298527

1'-(Cyclopropylmethyl)-6-methoxyspiro[1,2,3,4-tetrahydronaphthalene-2,4'-piperidin]-1-one



C₁₉ H₂₅ N O₂; Mol wt: 299.4115

ACTION – Agent for the treatment of pain, particularly neuropathic pain and diabetic neuropathy, as well as other CNS disorders such as seizures, a neuronal sodium channel antagonist. *In vitro*, compound inhibited [³H]-batrachotoxin binding in rat cortical homogenates (K_i = 3890 nM), as well as veratridine-stimulated ²²Na⁺ influx into SK-N-SH neuroblastoma cells (IC₅₀ = 30 μM). *In vivo*, it exhibited potent analgesic activity in the PGE₂-induced chronic hyperalgesia (Randall-Selitto) assay in rats (100% inhibition at 10 mg/kg s.c.). Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
298528	H	H	H	cyclopropyl-CH2	C ₁₈ H ₂₃ NO
298529	H	H	H	cyclopropyl-CH2CH2	C ₁₉ H ₂₅ NO
298530	H	H	H	CH2CH=CHPh	C ₂₃ H ₂₅ NO
298531	H	H	H	CH2CH2CH(Ph)2	C ₂₉ H ₃₁ NO
298532	H	H	H	(CH2)3Ph	C ₂₃ H ₂₇ NO
298533	OMe	H	H	cyclobutyl-CH2	C ₂₀ H ₂₇ NO ₂
298534	H	OMe	H	cyclopropyl-CH2CH2	C ₂₀ H ₂₇ NO ₂
298535	H	OMe	H	cyclobutyl-CH2	C ₂₀ H ₂₇ NO ₂
298536	H	OMe	H	(CH2)3Ph	C ₂₄ H ₂₉ NO ₂
298537	H	H	OMe	cyclopropyl-CH2CH2	C ₂₀ H ₂₇ NO ₂
298538	H	OMe	H	H	C ₁₅ H ₁₅ NO ₂

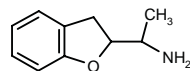
SOURCE – Pfizer.

REFERENCES

1. Calvet, A. et al. (Pfizer Inc.) *Tricyclic analgesics*. WO 0075116.

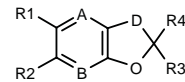
299073

1-(2,3-Dihydrobenzofuran-2-yl)ethylamine



C10 H13 N O; Mol wt: 163.2187

ACTION – Antinociceptive agent, a I₂ receptor ligand and/or sodium channel blocker reported to exhibit good analgesic properties, for example, in the mouse formalin test and in the rat Chung model, being particularly effective in the treatment of chronic pain. Other aminoalkyl substituted heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	A	B	D	Formula
299074	NO2	H	CH(Me)NH2	H	CH	CH	-CH2-	C ₁₀ H ₁₂ N ₂ O ₃
299075	H	H	CH(Me)NH-CH2CH2N(Et)2	H	CH	C(MeO)	-CH2-	C ₁₇ H ₂₈ N ₂ O ₂
299076	H	H	C(Me)2NHEt	H	CH	CH	-CH2-	C ₁₃ H ₁₉ NO
299077	H	H	CH2NH2	Me	CH	CH	-CH2-	C ₁₀ H ₁₃ NO
299078	Me	H	CH(Me)NH2	H	N	CH	-CH2-	C ₁₀ H ₁₄ N ₂ O
299080	Me	H	CH(Me)NH2	H	CH	N	-CH2-	C ₁₀ H ₁₄ N ₂ O
299081	H	OMe	CH(Me)NH2	H	CH	CH	-(CH2)2-	C ₁₂ H ₁₇ NO ₂

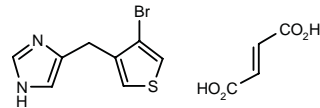
SOURCE – AstraZeneca.

REFERENCES

1. Besidski, Y. and Swahn, B.-M. (AstraZeneca AB) *New cpds*. WO 0076990.

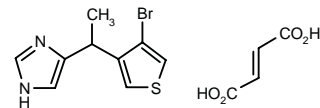
300642

4-(4-Bromo-3-thienylmethyl)-1H-imidazole fumarate



C8 H7 Br N2 S . C4 H4 O4; Mol wt: 359.1989

ACTION – Analgesic agent, a high-affinity ligand for the α_{2D}-adrenoceptor (K_i = 0.23 nM) with antinociceptive activity in the rat abdominal irritant test (ED₅₀ = 0.38 mg/kg p.o.). Compound showed few cardiovascular side effects at a dose 3-fold its ED₅₀ for antinociceptive activity. Another related compound is:



300644: C9 H9 Br N2 S . C4 H4 O4

SOURCE – Johnson & Johnson.

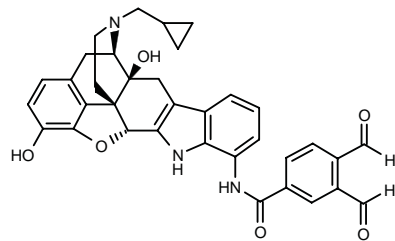
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1. Boyd, R.E. et al. α₂ Adrenoceptor agonists as potential analgesic agents. 3. Imidazolylmethylthiophenes. J Med Chem 2001, 44(6): 863.

PNTI

292725

N-(Cyclopropylmethyl)-4,5 α -epoxy-7'-(3,4-diformylbenzamido)-6,7-didehydroindolo[2',3':6,7]morphinan-3,14 β -diol



C35 H31 N3 O6; Mol wt: 589.6449

ACTION – Potent delta opioid receptor agonist, a naltrindole derivative that shows full agonist activity in the mouse vas deferens assay (IC₅₀ = 0.12 nM) and is 2-fold more potent than the reference delta opioid receptor agonist [D-Ala²,D-Leu⁵]-enkephalin. *In vivo* in the mouse tail-flick test, compound produced a dose- and time-dependent analgesic effect (ED₅₀ = 2.06 nmol/mouse), an effect antagonized by the selective delta opioid receptor antagonist naltrindole but not by the selective mu and kappa opioid receptor antagonists β -funaltrexamine and norbinaltorphimine. Potentially useful as a tool to investigate the delta opioid receptor recognition site.

SOURCE – University of Minnesota, Minneapolis, MN (US).

REFERENCES

1. Le Bourdonnec, B. et al. 7'-Phthalaldehydecaboxamidonaltrindole (PNTI): A potent selective non-peptidic delta opioid receptor agonist. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 233.

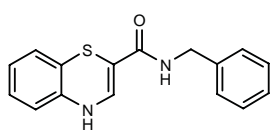
2. Le Bourdonnec, B. et al. Covalently induced activation of the delta opioid receptor by a fluorogenic affinity label, 7'-(phthalaldehyde-carboxamido)naltrindole (PNTI). J Med Chem 2001, 44(7): 1017.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

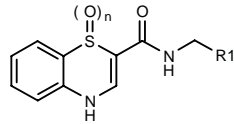
298041

N-Benzyl-4*H*-1,4-benzothiazine-2-carboxamide



C16 H14 N2 O S; Mol wt: 282.3656

ACTION – Potent and selective GABA_A receptor ligand that acts as an agonist, antagonist or inverse agonist at brain GABA_A receptors and is thus expected to be useful for the treatment of anxiety, depression, benzodiazepine overdose, Down's syndrome, sleep and cognition disorders, among others. A representative compound from a series of 4*H*-1,4-benzothiazine-2-carboxamides wherein the following are also included:



Compound	R1	n	Formula
298042	Ph	2	C ₁₆ H ₁₄ N ₂ O ₃ S
298043	2-MeO-Ph	1	C ₁₇ H ₁₆ N ₂ O ₃ S
298044	3-Cl-Ph	1	C ₁₆ H ₁₃ ClN ₂ O ₂ S
298045	4-Me-Ph	1	C ₁₇ H ₁₆ N ₂ O ₂ S
298046	1,3-benzodioxol-5-yl	1	C ₁₇ H ₁₄ N ₂ O ₄ S
298047	2-F-4-PrO-Ph	1	C ₁₉ H ₁₉ FN ₂ O ₃ S
298048	Pr	1	C ₁₃ H ₁₆ N ₂ O ₂ S
298049	2-furyl	2	C ₁₄ H ₁₂ N ₂ O ₄ S
298051	2-SH-Ph	2	C ₁₆ H ₁₄ N ₂ O ₃ S ₂
298052	CH ₂ CH ₂ OEt	2	C ₁₄ H ₁₈ N ₂ O ₄ S

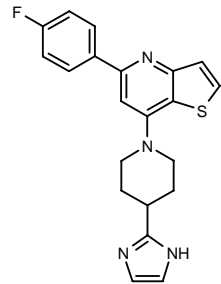
SOURCE – Neurogen.

REFERENCES

1. Cai, G. et al. (Neurogen Corp.) 4*H*-1,4-Benzothiazine-2-carboxamides and their use as GABA brain receptor ligands. WO 0071528.

299034

5-(4-Fluorophenyl)-7-[4-(1*H*-imidazol-2-yl)piperidin-1-yl]thieno[3,2-*b*]pyridine



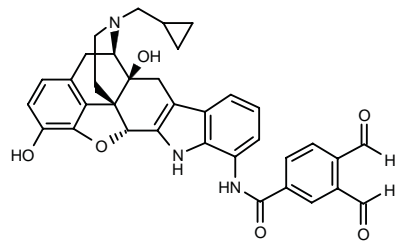
C21 H19 F N4 S; Mol wt: 378.4731

ACTION – Agent that binds with high affinity and selectivity to the benzodiazepine site of brain GABA_A receptors, potentially useful for the treatment of anxiety, depression, sleep disorders and cognitive impairment. Other specifically claimed compounds from this series of aryl and heteroaryl substituted pyridino derivatives are:

PNTI

292725

N-(Cyclopropylmethyl)-4,5 α -epoxy-7'-(3,4-diformylbenzamido)-6,7-didehydroindolo[2',3':6,7]morphinan-3,14 β -diol



C35 H31 N3 O6; Mol wt: 589.6449

ACTION – Potent delta opioid receptor agonist, a naltrindole derivative that shows full agonist activity in the mouse vas deferens assay (IC₅₀ = 0.12 nM) and is 2-fold more potent than the reference delta opioid receptor agonist [D-Ala²,D-Leu⁵]-enkephalin. *In vivo* in the mouse tail-flick test, compound produced a dose- and time-dependent analgesic effect (ED₅₀ = 2.06 nmol/mouse), an effect antagonized by the selective delta opioid receptor antagonist naltrindole but not by the selective mu and kappa opioid receptor antagonists β -funaltrexamine and norbinaltorphimine. Potentially useful as a tool to investigate the delta opioid receptor recognition site.

SOURCE – University of Minnesota, Minneapolis, MN (US).

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1. Le Bourdonnec, B. et al. 7'-Phthalaldehydecaboxamidonaltrindole (PNTI): A potent selective non-peptidic delta opioid receptor agonist. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 233.

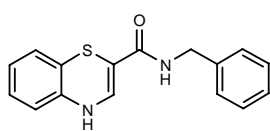
2. Le Bourdonnec, B. et al. Covalently induced activation of the delta opioid receptor by a fluorogenic affinity label, 7'-(phthalaldehyde-carboxamido)naltrindole (PNTI). J Med Chem 2001, 44(7): 1017.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

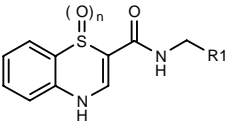
298041

N-Benzyl-4*H*-1,4-benzothiazine-2-carboxamide



C16 H14 N2 O S; Mol wt: 282.3656

ACTION – Potent and selective GABA_A receptor ligand that acts as an agonist, antagonist or inverse agonist at brain GABA_A receptors and is thus expected to be useful for the treatment of anxiety, depression, benzodiazepine overdose, Down's syndrome, sleep and cognition disorders, among others. A representative compound from a series of 4*H*-1,4-benzothiazine-2-carboxamides wherein the following are also included:



Compound	R1	n	Formula
298042	Ph	2	C ₁₆ H ₁₄ N ₂ O ₃ S
298043	2-MeO-Ph	1	C ₁₇ H ₁₆ N ₂ O ₃ S
298044	3-Cl-Ph	1	C ₁₆ H ₁₃ ClN ₂ O ₂ S
298045	4-Me-Ph	1	C ₁₇ H ₁₆ N ₂ O ₂ S
298046	1,3-benzodioxol-5-yl	1	C ₁₇ H ₁₄ N ₂ O ₄ S
298047	2-F-4-PrO-Ph	1	C ₁₉ H ₁₉ FN ₂ O ₃ S
298048	Pr	1	C ₁₃ H ₁₆ N ₂ O ₂ S
298049	2-furyl	2	C ₁₄ H ₁₂ N ₂ O ₄ S
298051	2-SH-Ph	2	C ₁₆ H ₁₄ N ₂ O ₃ S ₂
298052	CH ₂ CH ₂ OEt	2	C ₁₄ H ₁₈ N ₂ O ₄ S

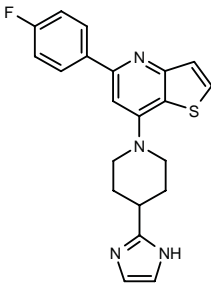
SOURCE – Neurogen.

REFERENCES

1. Cai, G. et al. (Neurogen Corp.) 4*H*-1,4-Benzothiazine-2-carboxamides and their use as GABA brain receptor ligands. WO 0071528.

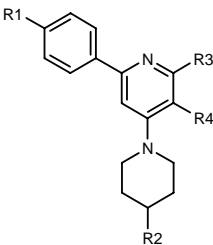
299034

5-(4-Fluorophenyl)-7-[4-(1*H*-imidazol-2-yl)piperidin-1-yl]thieno[3,2-*b*]pyridine



C21 H19 F N4 S; Mol wt: 378.4731

ACTION – Agent that binds with high affinity and selectivity to the benzodiazepine site of brain GABA_A receptors, potentially useful for the treatment of anxiety, depression, sleep disorders and cognitive impairment. Other specifically claimed compounds from this series of aryl and heteroaryl substituted pyridino derivatives are:



Compound	R1	R2	R3,R4	Formula
299035	H	2-imidazolyl	-CH=CHCH=CH-	C ₂₃ H ₂₂ N ₄
299036	F	2-imidazolyl	-CH=CHCH=CH-	C ₂₃ H ₂₁ FN ₄
299037	F	CONH2	-CH=CHS-	C ₁₉ H ₁₈ FN ₃ OS
299038	F	4H-1,2,4-triazol-3-yl	-CH=CHS-	C ₂₀ H ₁₈ FN ₅ S
299215	H	4H-1,2,4-triazol-3-yl	-CH=CHCH=CH-	C ₂₂ H ₂₁ N ₅
299216	H	5-Me-2-imidazolyl	-CH=CHCH=CH-	C ₂₄ H ₂₄ N ₄

SOURCE – Neurogen.

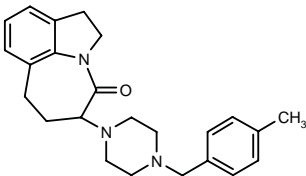
REFERENCES

1. Cai, G. et al. (Neurogen Corp.) *Aryl and heteroaryl subst. pyridino derivs.; GABA brain receptor ligands*. WO 0077008.

ANTIPSYCHOTIC DRUGS

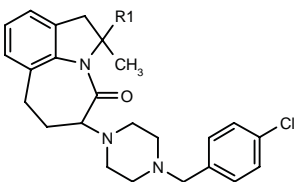
299024

5-[4-(4-Methylbenzyl)piperazin-1-yl]-1,2,4,5,6,7-hexahydroazepino[3,2,1-*h*]indol-4-one



C24 H29 N3 O; Mol wt: 375.5131

ACTION – Potent dopamine D4 receptor modulator with selectivity over D2 receptors and α₁-adrenoceptors, as demonstrated in binding assays by K_i values of 4, 136 and 1095 nM, respectively, for the human D4, primate D2 and human α₁ receptors expressed in CHO cells. Claimed for the treatment or prevention of schizophrenia, psychotic depression, obsessive–compulsive disorder, mania, Parkinson’s disease, tardive dyskinesia, attention deficit disorder, Alzheimer’s disease and extrapyramidal side effects associated with the use of neuroleptic agents. Other exemplified compounds from this series of 1-azatricyclic-4-benzylpiperazines include the following:



Compound	R1	Formula
299025	Me	C ₂₅ H ₃₀ ClN ₃ O
299026	H	C ₂₄ H ₂₈ ClN ₃ O

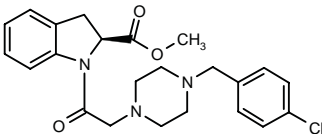
SOURCE – Neurogen.

REFERENCES

1. Zhang, S. et al. (Neurogen Corp.) *1-Azatricyclic-4-benzylpiperazines*. WO 0077004.

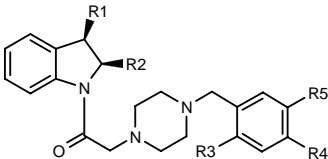
299027

1-[2-[4-(4-Chlorobenzyl)piperazin-1-yl]acetyl]-2,3-dihydro-1*H*-indole-2(*S*)-carboxylic acid methyl ester



C23 H26 Cl N3 O3; Mol wt: 427.9294

ACTION – Potent dopamine D4 receptor modulator with selectivity over D2 receptors, as demonstrated in binding assays by K_i values of 5 and 1178 nM, respectively, for the human D4 and primate D2 subtypes expressed in CHO cells. Claimed for the treatment or prevention of schizophrenia, psychotic depression, obsessive–compulsive disorder, mania, Parkinson’s disease, tardive dyskinesia, attention deficit disorder, Alzheimer’s disease and extrapyramidal side effects associated with the use of neuroleptic agents. Other exemplified compounds from this series of benzylpiperazinyl-indolinylethanones include the following:



Compound	R1	R2	R3	R4	R5	Formula
299028	Me	Me	OMe	H	Cl	C ₂₄ H ₃₀ ClN ₃ O ₂
299029	H	vinyl	H	Cl	H	C ₂₃ H ₂₆ ClN ₃ O
299030	-(CH2)4-		H	Me	H	C ₂₆ H ₃₃ N ₃ O

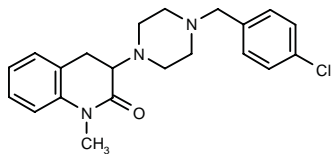
SOURCE – Neurogen.

REFERENCES

1. Zhao, H. and Thurkauf, A. (Neurogen Corp.) *Benzylpiperazinyl-indolinylethanones*. WO 0076967.

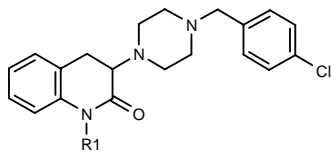
299031

3-[4-(4-Chlorobenzyl)piperazin-1-yl]-1-methyl-1,2,3,4-tetrahydroquinolin-2-one



C21 H24 Cl N3 O; Mol wt: 369.8936

ACTION – Potent dopamine D4 receptor modulator with selectivity over D2 receptors, as demonstrated in binding assays by K_i values of 6 and 144 nM, respectively, for the human D4 and primate D2 receptors expressed in CHO cells. Claimed for the treatment or prevention of schizophrenia, psychotic depression, obsessive–compulsive disorder, mania, Parkinson’s disease, tardive dyskinesia, attention deficit disorder, Alzheimer’s disease and extrapyramidal side effects associated with the use of neuroleptic agents. Other exemplified compounds from this series of piperidinyl and piperazinyl substituted benzofused lactams include the following:



Compound	R1	Formula
299032	Et	C ₂₂ H ₂₆ ClN ₃ O
299033	H	C ₂₀ H ₂₂ ClN ₃ O

SOURCE – Neurogen.

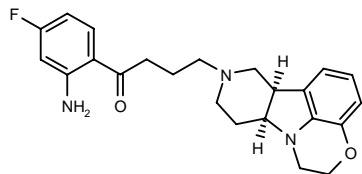
REFERENCES

1. Zhao, H. and Thurkauf, A. (Neurogen Corp.) *Piperidinyl and piperazinyl substd. benzofused lactams*. WO 0076981.

IT-657

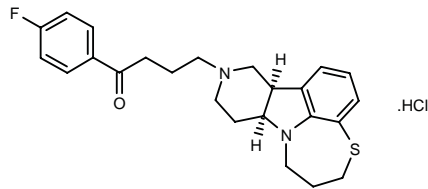
301825

1-(2-Amino-4-fluorophenyl)-4-[(6b*R*,10a*S*)-1,2,6b,9,10,10a-hexahydropyrido[3',4':4,5]pyrrolo[1,2,3-*de*][1,4]-benzoxazin-8(7*H*)-yl]butan-1-one



C23 H26 F N3 O2; Mol wt: 395.4754

ACTION – Potential antipsychotic agent, a potent 5-HT_{2A}/dopamine D2 receptor antagonist (K_i = 0.2 and 2.3 nM, respectively in binding studies) with high selectivity over 5-HT_{2C}, 5-HT_{1A}, dopamine D4 and D5 receptors, as well as α_1 -adrenoceptors (K_i = 128, 909, 29, 2580 and 118 nM, respectively). Compound showed good oral bioavailability and exhibited excellent efficacy *in vivo* in inhibiting quipazine-induced head twitches in rats (ED₅₀ = 0.03 mg/kg p.o.). Another tetracyclic indoline butyro-phenone analogue is:



SX-477 [301824]: C24 H27 F N2 O S . H Cl

SOURCE – DuPont Pharmaceuticals.

REFERENCES

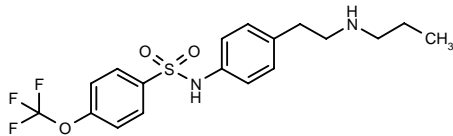
1. Robichaud, A.J. et al. (DuPont Pharmaceuticals Co.) *Substd. heterocycle fused γ -carboline*s. WO 0077001, WO 0077002, WO 0077010.

2. Lee, T. et al. *Novel, highly potent and selective serotonin 5-HT_{2A}/dopamine D2 receptor antagonists as potential antipsychotics*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 98.

PNU-177864*

283185

N-[4-[2-(Propylamino)ethyl]phenyl]-4-(trifluoromethoxy)-benzenesulfonamide



C18 H21 F3 N2 O3 S; Mol wt: 402.4349

ACTION – Selective, orally active and metabolically stable dopamine D3 antagonist, selected for clinical studies as a potential antipsychotic agent.

SOURCE – Pharmacia.

REFERENCES

1. Romero, A.G. and Leiby, J.A. (Pharmacia Corp.) *Phenylsulfonamide-phenyl-ethylamines useful as dopamine receptors*. EP 1077935, WO 9958499.

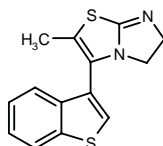
2. Romero, A.G. et al. *Discovery of the potential antipsychotic PNU-177864, a selective dopamine D3 receptor antagonist, using high-throughput analoging techniques*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 170.

*Identified compound **283185** (see **283181**) Drug Data Rep 2000, 022(01): 0018.

TREATMENT OF MOOD DISORDERS

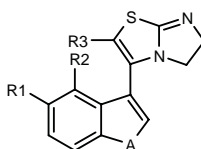
297934

3-(3-Benzothieryl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]-thiazole



C₁₄ H₁₂ N₂ S₂; Mol wt: 272.3948

ACTION – Combined 5-HT_{1A} receptor agonist and 5-HT and noradrenaline reuptake inhibitor, with potential in the treatment of depression, anxiety, psychoses, tardive dyskinesia, obesity, drug addiction, cognitive disorders, Alzheimer's disease, cerebral ischemia, obsessive-compulsive behavior, panic attacks, social phobias, bulimia, anorexia, non-insulin-dependent diabetes mellitus, hyperglycemia, hyperlipidemia and stress, as an aid in smoking cessation and in the treatment or prevention of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, head injuries and hemorrhage. *In vitro*, compound exhibited a K_i value of 5.6 nM against [³H]-8-OH-DPAT binding to 5-HT_{1A} receptors from rat hippocampal tissue and inhibited 5-HT and noradrenaline uptake in rat cortical tissue with K_i values of 266 and 3.1 nM, respectively, while exhibiting weaker affinity for muscarinic receptors (K_i = 352 nM). In addition, it exhibited reduced monoamine oxidase A (MAO-A)-inhibitory activity compared to structurally related compounds, with an IC₅₀ value of 1600 nM. *In vivo*, it was shown to reduce food intake in rats, giving an ED₅₀ value of 1.1 mg/kg p.o. at 2 h. Other specifically claimed compounds from this series of substituted imidazothiazoles are:



Compound	R1	R2	R3	A	Formula
297935	Cl	H	Me	S	C ₁₄ H ₁₁ ClN ₂ S ₂
297936	H	F	Me	S	C ₁₄ H ₁₁ FN ₂ S ₂
297937	H	H	Et	S	C ₁₅ H ₁₄ N ₂ S ₂
297939	Me	H	Me	S	C ₁₅ H ₁₄ N ₂ S ₂
297940	H	H	i-Pr	S	C ₁₆ H ₁₆ N ₂ S ₂
297941	SMe	H	Me	S	C ₁₅ H ₁₄ N ₂ S ₃
297942	F	H	Me	S	C ₁₄ H ₁₁ FN ₂ S ₂
297943	Cl	H	Et	S	C ₁₅ H ₁₃ ClN ₂ S ₂
297944	Br	H	Me	S	C ₁₄ H ₁₁ BrN ₂ S ₂
297945	H	H	Me	O	C ₁₄ H ₁₂ N ₂ OS

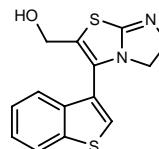
SOURCE – Knoll (Abbott).

REFERENCES

1. Brough, P.A. et al. (Knoll AG) *Subst. imidazothiazoles as antidepressant agents*. WO 0071548.

297946

1-[3-(3-Benzothieryl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol



C₁₄ H₁₂ N₂ O S₂; Mol wt: 288.3938

ACTION – Combined 5-HT_{1A} receptor agonist and 5-HT and noradrenaline reuptake inhibitor, with potential in the treatment of depression, anxiety, psychoses, tardive dyskinesia, obesity, drug addiction, cognitive disorders, Alzheimer's disease, cerebral ischemia, obsessive-compulsive behavior, panic attacks, social phobias, bulimia, anorexia, non-insulin-dependent diabetes mellitus, hyperglycemia, hyperlipidemia and stress, as an aid in smoking cessation and in the treatment or prevention of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, head injuries and hemorrhage. *In vitro*, compound exhibited a K_i value of 11 nM against [³H]-8-OH-DPAT binding to 5-HT_{1A} receptors from rat hippocampal tissue and inhibited 5-HT and noradrenaline uptake in rat cortical tissue with K_i values of 162 and 3.1 nM, respectively, while exhibiting weaker affinity for muscarinic receptors (16% inhibition at 1 μM).

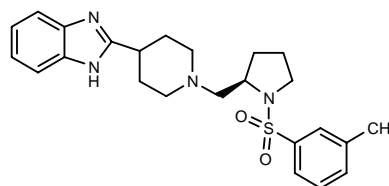
SOURCE – Knoll (Abbott).

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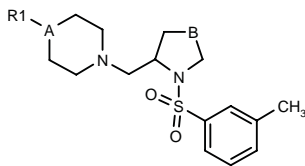
298222

2-[1-[1-(3-Methylphenylsulfonyl)pyrrolidin-2(*R*)-ylmethyl]-piperidin-4-yl]-1*H*-benzimidazole



C₂₄ H₃₀ N₄ O₂ S; Mol wt: 438.5930

ACTION – Agent for the treatment or prevention of CNS disorders, particularly depression and sleep disorders, with 5-HT₇ receptor-antagonist activity. Other exemplified compounds from this series of sulfonamide derivatives include the following:



Compound	R1	A	B	Isomer	Formula
298223	5-F-2-benzimidazolyl	CH	-CH2-	R	C ₂₄ H ₂₉ FN ₄ O ₂ S
298224	2-benzoxazolyl	CH	-CH2-	R	C ₂₄ H ₂₉ N ₃ O ₃ S
298225	2-benzimidazolyl	N	-CH2-	R	C ₂₃ H ₂₉ N ₅ O ₂ S
298226	2-MeO-Ph	N	-CH2-	R	C ₂₃ H ₃₁ N ₃ O ₃ S
298227	3-indolyl	CH	-CH2-	R	C ₂₅ H ₃₁ N ₃ O ₂ S
298228	2-benzimidazolyl	CH	-CH2-	S	C ₂₄ H ₃₀ N ₄ O ₂ S
298229	5-F-2-benzimidazolyl	CH	-CH2-	S	C ₂₄ H ₂₉ FN ₄ O ₂ S
298230	2-benzoxazolyl	CH	-CH2-	S	C ₂₄ H ₂₉ N ₃ O ₃ S
298231	2-benzimidazolyl	N	-CH2-	S	C ₂₃ H ₂₉ N ₅ O ₂ S
298232	2-MeO-Ph	N	-CH2-	S	C ₂₃ H ₃₁ N ₃ O ₃ S
298233	3-indolyl	CH	-CH2-	S	C ₂₅ H ₃₁ N ₃ O ₂ S
298483	2-benzimidazolyl	CH	-(CH2)2-		C ₂₅ H ₃₂ N ₄ O ₂ S

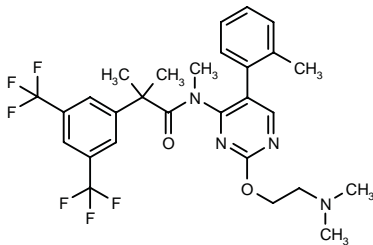
SOURCE – GlaxoSmithKline.

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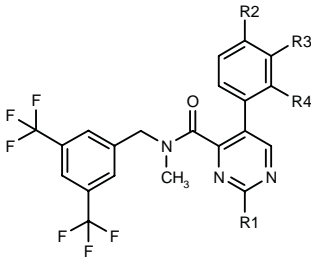
298346

2-[3,5-Bis(trifluoromethyl)phenyl]-N-[2-[2-(dimethyl-amino)ethoxy]-5-(2-methylphenyl)pyrimidin-4-yl]-N,2-dimethylpropionamide



C28 H30 F6 N4 O2; Mol wt: 568.5590

ACTION – Tachykinin NK₁ receptor antagonist (pK_i = 9.18), preferably indicated for the treatment of depressive disorders and emesis. Other exemplified 5-phenyl-pyrimidine derivatives are:



Compound	R1	R2	R3	R4	Formula
298347	4-Me-1-Piz	H	H	Cl	C ₂₆ H ₂₄ ClF ₆ N ₅ O
298348	OCH2CH2N(Me)2	H	H	Me	C ₂₆ H ₂₆ F ₆ N ₄ O ₂
298349	4-Me-1-Piz	H	-CH=CHCH=CH-		C ₃₀ H ₂₇ F ₆ N ₅ O
298350	NHCH2CH2N(Me)2	F	H	Me	C ₂₆ H ₂₆ F ₇ N ₅ O

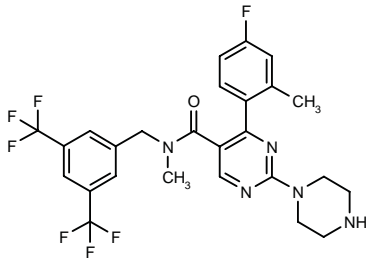
SOURCE – Roche.

REFERENCES

1. Boes, M. et al. (F. Hoffmann-La Roche AG) *5-Phenyl-pyrimidine derivs.* WO 0073278.

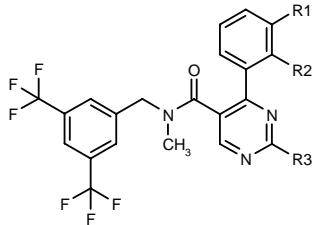
298351

N-[3,5-Bis(trifluoromethyl)benzyl]-4-(4-fluoro-2-methyl-phenyl)-N-methyl-2-(1-piperazinyl)pyrimidine-5-carbox-amide



C26 H24 F7 N5 O; Mol wt: 555.4956

ACTION – Tachykinin NK₁ receptor antagonist (pK_i = 9.14), preferably indicated for the treatment of depressive disorders and emesis. Other exemplified 4-phenyl-pyrimidine derivatives are:



Compound	R1	R2	R3	Formula
298352	H	Cl	OCH2CH2N(Me)2	C ₂₅ H ₂₃ ClF ₆ N ₄ O ₂
298353	H	Cl	O(CH2)3N(Me)2	C ₂₆ H ₂₅ ClF ₆ N ₄ O ₂
298354	-CH=CHCH=CH-		4-Me-1-Piz	C ₃₀ H ₂₇ F ₆ N ₅ O

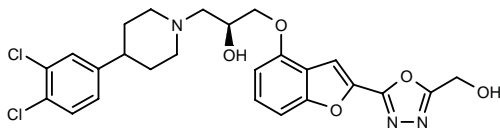
SOURCE – Roche.

REFERENCES

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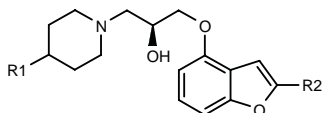
298445

1-[4-(3,4-Dichlorophenyl)piperidin-1-yl]-3-[2-[5-(hydroxy-methyl)-1,3,4-oxadiazol-2-yl]benzofuran-4-yloxy]propan-2(S)-ol



C25 H25 Cl2 N3 O5; Mol wt: 518.3945

ACTION – Antidepressant, a combined 5-HT_{1A} receptor antagonist ($K_i = 0.37$ nM against [³H]-8-OH-DPAT binding in rat hippocampal preparations) and 5-HT reuptake inhibitor ($K_i = 0.18$ nM for inhibition of [³H]-paroxetine binding in rat cortical membranes). Compound is further reported to antagonize 8-OH-DPAT-induced hypothermia in mice at 0.1-100 mg/kg p.o., as well as to significantly shorten immobility time in comparison with selective serotonin reuptake inhibitors (SSRIs) in a forced swimming test in mice at doses of 1-100 mg/kg p.o., indicating potential as a fast-acting antidepressant. Other exemplified compounds from this series of phenoxypropylamine derivatives include the following:



Compound	R1	R2	Formula
298446	2-Naph	CON(Me)OMe	C ₂₉ H ₃₂ N ₂ O ₅
298448	3,4-(Cl)2-Ph	5-Me-1,3,4-oxadiazol-2-yl	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₄
298449	1,3-benzodioxol-5-yl	5-i-Pr-1,3,4-oxadiazol-2-yl	C ₂₈ H ₃₁ N ₃ O ₆

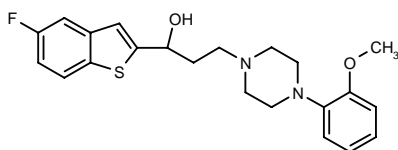
SOURCE – Welfide.

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1. Nishiyama, A. et al. (Welfide Corp.) *Phenoxypropylamine cpds.* WO 0071517.

300859

1-(5-Fluorobenzothien-2-yl)-3-[4-(2-methoxyphenyl)-piperazin-1-yl]propan-1-ol



C₂₂ H₂₅ F N₂ O₂ S; Mol wt: 400.5155

ACTION – Arylpiperazine derivative with affinity for both 5-HT_{1A} receptors and the 5-HT transporter ($K_i = 2.3$ and 12 nM, respectively) and functional antagonist activity at 5-HT_{1A} receptors ($IC_{50} = 14$ nM for inhibition of 8-OH-DPAT-stimulated GTP γ S binding in rat hippocampus). Potential lead in the development of new antidepressant.

SOURCES – Universidad de Navarra, Pamplona (ES); Vita.

REFERENCES

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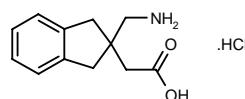
2. Martinez, J. et al. *New 3-[4-(aryl)piperazin-1-yl]-1-(benzo[b]thiophen-3-yl)propane derivatives with dual action at 5-HT_{1A} serotonin receptors and serotonin transporter as a new class of antidepressants.* Eur J Med Chem 2001, 36(1): 55.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

298216

2-[2-(Aminomethyl)-2,3-dihydro-1H-inden-2-yl]acetic acid hydrochloride



C₁₂ H₁₅ N O₂ . HCl; Mol wt: 241.7164

ACTION – Agent for the treatment of epilepsy and other neurological and CNS disorders, including faintness attacks, hypokinesia, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders and sleep disorders with good binding affinity for the Ca²⁺ channel $\alpha 2$ - δ subunit ($IC_{50} = 0.059$ μ M vs. 0.10-0.12 μ M for gabapentin) and which is thus expected to have similar pharmacological effects to gabapentin. *In vivo*, compound was active in the carrageenan-induced thermal hyperalgesia assay in rats at 30 mg/kg p.o. A representative compound from a series of fused polycyclic amino acids.

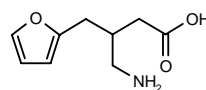
SOURCE – Pfizer.

REFERENCES

1. Bryans, J.S. et al. (Pfizer Inc.) *Fused polycyclic amino acids as pharmaceutical agents.* WO 0073259.

298217

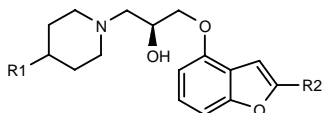
4-Amino-3-(2-furylmethyl)butyric acid



C₉ H₁₃ N O₃; Mol wt: 183.2057

ACTION – Agent for the treatment of epilepsy, faintness attacks, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders and inflammation, with affinity for the Ca²⁺ channel $\alpha 2$ - δ subunit ($IC_{50} = 0.421$ μ M vs. 0.10-0.12 μ M for gabapentin) and which is thus expected to have similar pharmacological effects to gabapentin. *In vivo*, compound was active in the carrageenan-induced thermal hyperalgesia assay in rats and in the audiogenic seizure model in DBA/2 mice following oral administration. Other exemplified compounds from this series of 3-heteroarylalkyl substituted GABA analogues include the following:

ACTION – Antidepressant, a combined 5-HT_{1A} receptor antagonist ($K_i = 0.37$ nM against [³H]-8-OH-DPAT binding in rat hippocampal preparations) and 5-HT reuptake inhibitor ($K_i = 0.18$ nM for inhibition of [³H]-paroxetine binding in rat cortical membranes). Compound is further reported to antagonize 8-OH-DPAT-induced hypothermia in mice at 0.1-100 mg/kg p.o., as well as to significantly shorten immobility time in comparison with selective serotonin reuptake inhibitors (SSRIs) in a forced swimming test in mice at doses of 1-100 mg/kg p.o., indicating potential as a fast-acting antidepressant. Other exemplified compounds from this series of phenoxypropylamine derivatives include the following:



Compound	R1	R2	Formula
298446	2-Naph	CON(Me)OMe	C ₂₉ H ₃₂ N ₂ O ₅
298448	3,4-(Cl)2-Ph	5-Me-1,3,4-oxadiazol-2-yl	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₄
298449	1,3-benzodioxol-5-yl	5-i-Pr-1,3,4-oxadiazol-2-yl	C ₂₈ H ₃₁ N ₃ O ₆

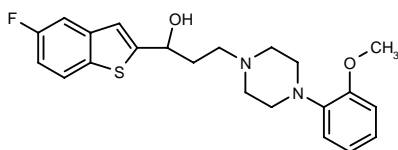
SOURCE – Welfide.

REFERENCES

1. Nishiyama, A. et al. (Welfide Corp.) *Phenoxypropylamine cpds.* WO 0071517.

300859

1-(5-Fluorobenzothien-2-yl)-3-[4-(2-methoxyphenyl)-piperazin-1-yl]propan-1-ol



C₂₂ H₂₅ F N₂ O₂ S; Mol wt: 400.5155

ACTION – Arylpiperazine derivative with affinity for both 5-HT_{1A} receptors and the 5-HT transporter ($K_i = 2.3$ and 12 nM, respectively) and functional antagonist activity at 5-HT_{1A} receptors ($IC_{50} = 14$ nM for inhibition of 8-OH-DPAT-stimulated GTP γ S binding in rat hippocampus). Potential lead in the development of new antidepressant.

SOURCES – Universidad de Navarra, Pamplona (ES); Vita.

REFERENCES

1. Monge Vega, A. et al. (Laboratorios Vita, SA) *Cpds. derived from thiophene and benzothiophene, and related utilisation and compsn.* EP 1008594, ES 2128266, WO 9902516.

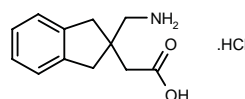
2. Martinez, J. et al. *New 3-[4-(aryl)piperazin-1-yl]-1-(benzo[b]thiophen-3-yl)propane derivatives with dual action at 5-HT_{1A} serotonin receptors and serotonin transporter as a new class of antidepressants.* Eur J Med Chem 2001, 36(1): 55.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

298216

2-[2-(Aminomethyl)-2,3-dihydro-1H-inden-2-yl]acetic acid hydrochloride



C₁₂ H₁₅ N O₂ . HCl; Mol wt: 241.7164

ACTION – Agent for the treatment of epilepsy and other neurological and CNS disorders, including faintness attacks, hypokinesia, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders and sleep disorders with good binding affinity for the Ca²⁺ channel $\alpha 2$ - δ subunit ($IC_{50} = 0.059$ μ M vs. 0.10-0.12 μ M for gabapentin) and which is thus expected to have similar pharmacological effects to gabapentin. *In vivo*, compound was active in the carrageenan-induced thermal hyperalgesia assay in rats at 30 mg/kg p.o. A representative compound from a series of fused polycyclic amino acids.

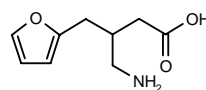
SOURCE – Pfizer.

REFERENCES

1. Bryans, J.S. et al. (Pfizer Inc.) *Fused polycyclic amino acids as pharmaceutical agents.* WO 0073259.

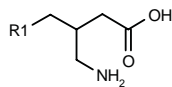
298217

4-Amino-3-(2-furylmethyl)butyric acid



C₉ H₁₃ N O₃; Mol wt: 183.2057

ACTION – Agent for the treatment of epilepsy, faintness attacks, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders and inflammation, with affinity for the Ca²⁺ channel $\alpha 2$ - δ subunit ($IC_{50} = 0.421$ μ M vs. 0.10-0.12 μ M for gabapentin) and which is thus expected to have similar pharmacological effects to gabapentin. *In vivo*, compound was active in the carrageenan-induced thermal hyperalgesia assay in rats and in the audiogenic seizure model in DBA/2 mice following oral administration. Other exemplified compounds from this series of 3-hetero-arylalkyl substituted GABA analogues include the following:



Compound	R1	Formula
298218	3-thienyl	C ₉ H ₁₃ NO ₂ S
298219	2-thienyl	C ₉ H ₁₃ NO ₂ S

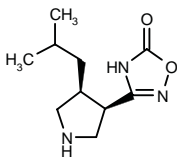
SOURCE – Pfizer.

REFERENCES

1. Yuen, P.-W. (Pfizer Inc.) 3-Heteroarylalkyl substd. GABA analogs. WO 0073296.

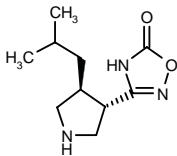
298220

cis-3-(4-Isobutylpyrrolidin-3-yl)-1,2,4-oxadiazol-5(4H)-one



C10 H17 N3 O2; Mol wt: 211.2633

ACTION – Agent for the treatment of epilepsy and other neurological and CNS disorders including faintness attacks, hypokinesia, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders and sleep disorders, with good binding affinity to the Ca²⁺ channel α 2- δ subunit and which is thus expected to have similar pharmacological effects to gabapentin. Another specifically claimed compound from this series of aminoheterocycles is:



298221: C10 H17 N3 O2

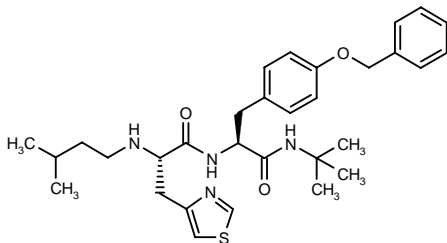
SOURCE – Pfizer.

REFERENCES

1. Belliotti, T.R. et al. (Pfizer Inc.) Amino heterocycles useful as pharmaceutical agents. WO 0073300.

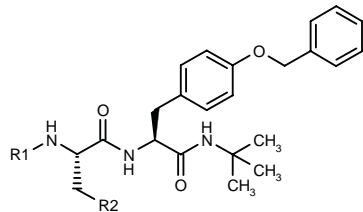
298430

N-(3-Methylbutyl)-3-(4-thiazolyl)-L-alanyl-O-benzyl-L-tyrosine *tert*-butylamide



C31 H42 N4 O3 S; Mol wt: 550.7638

ACTION – N-type calcium channel blocker, as demonstrated by 79% inhibition of calcium uptake at 1 μ M in the IMR32 assay, with potential for the treatment of epilepsy, stroke, cerebral ischemia, head trauma, asthma and amyotrophic lateral sclerosis. *In vivo*, compound exhibited potent anticonvulsant activity against audiogenic seizures in DBA/2 mice (100% protection at 30 mg/kg i.v.). Other exemplified compounds from this series of heteroarylalkyl α -substituted peptidylamine derivatives include the following:



Compound	R1	R2	Formula
298431	i-BuCH2	4-Pyr	C ₃₃ H ₄₄ N ₄ O ₃
298432	2-cyclohexenyl	4-Pyr	C ₃₄ H ₄₂ N ₄ O ₃
298433	i-BuCH2	3-Pyr	C ₃₃ H ₄₄ N ₄ O ₃
298434	2-cyclohexenyl	3-Pyr	C ₃₄ H ₄₂ N ₄ O ₃
298435	2-cyclohexenyl	4-thiazolyl	C ₃₂ H ₄₀ N ₄ O ₃ S
298436	cyclohexyl	4-thiazolyl	C ₃₂ H ₄₂ N ₄ O ₃ S
298437	cyclohexyl-CH2	4-imidazolyl	C ₃₃ H ₄₅ N ₅ O ₃
298438	i-Pr	4-imidazolyl	C ₂₉ H ₃₉ N ₅ O ₃

SOURCE – Pfizer.

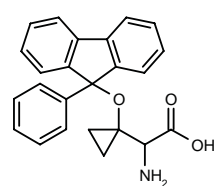
REFERENCES

1. Hu, L.-Y. et al. (Pfizer Inc.) Heteroaryl alkyl alpha substd. peptidylamine calcium channel blockers. US 6166052.

ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

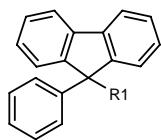
298138

2-Amino-2-[1-(9-phenyl-9H-fluoren-9-yloxy)cyclopropyl]-acetic acid



C24 H21 N O3; Mol wt: 371.4339

ACTION – Inhibitor of glycine transport via the GlyT-2 transporter, potentially useful for the treatment of conditions associated with increased or decreased muscle contraction, particularly pain or spasticity. Other specifically claimed tricyclic amino acid derivatives are:



Compound	R1	Formula
298139	CH2C(=CH2)CH(NH2)CO2H	C ₂₄ H ₂₁ NO ₂
298140	CH=CHCH(NH2)CO2H	C ₂₃ H ₁₉ NO ₂

SOURCE – NPS Allelix.

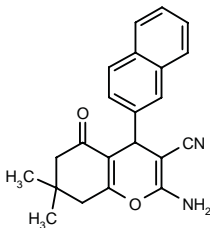
REFERENCES

1. Ognyanov, V.I. et al. (NPS Allelix Corp.) *Tricyclic amino-acid derivs.* US 6162824.

TREATMENT OF DISORDERS OF COGNITION

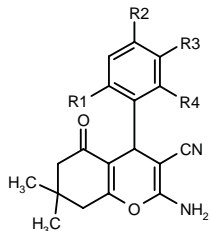
298664

2-Amino-7,7-dimethyl-4-(2-naphthalenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitrile



C22 H20 N2 O2; Mol wt: 344.4120

ACTION – An AMPA receptor potentiator, as demonstrated in an electrophysiological assay using rat AMPA receptors expressed in *Xenopus* oocytes, where it was found to potentiate AMPA response by 2-fold at a concentration of 1.6 μM. Potentially useful as a cognition enhancer, as well as for the treatment of neurodegenerative diseases (e.g., Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS-associated dementia and Down’s syndrome), schizophrenia and myoclonus. Other exemplified compounds from this series of substituted 5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyrans and benzothiopyrans include the following:



Compound	R1	R2	R3	R4	MF
298665	H	OMe	H	H	C ₁₉ H ₂₀ N ₂ O ₃
298666	Me	Me	H	Me	C ₂₁ H ₂₄ N ₂ O ₂
298667	H	-OCH2O-		H	C ₁₉ H ₁₈ N ₂ O ₄
298668	H	H	OMe	H	C ₁₉ H ₂₀ N ₂ O ₃

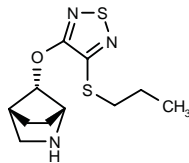
SOURCE – CoCensys.

REFERENCES

1. Konkoy, C.S. et al. (CoCensys, Inc.) *Substd. 5-oxo-5,6,7,8-tetrahydro-4H-1-benzopyrans and benzothiopyrans and the use thereof as potentiators of AMPA.* WO 0075123.

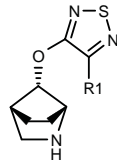
298686

endo-7-[4-(Propylsulfanyl)-1,2,5-thiadiazol-3-yloxy]-2-azabicyclo[2.2.1]heptane



C11 H17 N3 O S2; Mol wt: 271.4073

ACTION – Selective muscarinic M₄ receptor modulator with potential for the treatment of Alzheimer’s disease, psychosis, pain and schizophrenia, as well as for enhancing cognition. Other specifically claimed compounds within this series of 7-oxo-2-azabicyclo[2.2.1]-heptane derivatives include the following:



Compound	R1	Formula
298687	cyclopropyl-CH2O	C ₁₂ H ₁₇ N ₃ O ₂ S
298688	cyclopropyl-CH(Ph)CH2O	C ₁₉ H ₂₃ N ₃ O ₂ S
298689	OCH(CH2F)2	C ₁₁ H ₁₅ F ₂ N ₃ O ₂ S
298690	SBu	C ₁₂ H ₁₉ N ₃ OS ₂
298691	SC6H13	C ₁₄ H ₂₃ N ₃ OS ₂
298693	2-thienyl-CH2CH2O	C ₁₄ H ₁₇ N ₃ O ₂ S ₂
298694	cyclopropyl-CH2CH2O	C ₁₃ H ₁₉ N ₃ O ₂ S

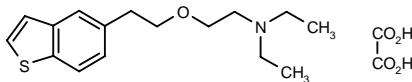
SOURCE – Lilly.

REFERENCES

1. Mitch, C.H. and Quimby, S.J. (Eli Lilly and Company) *7-Oxo-2-azabicyclo-[2.2.1]heptanes as selective muscarinic receptor antagonist.* WO 0075140.

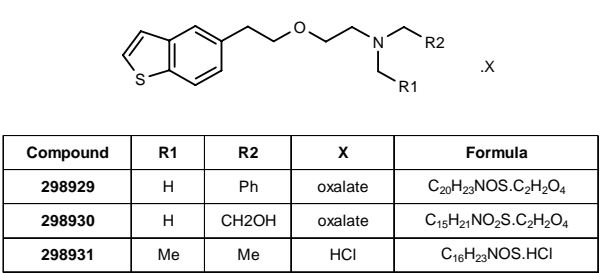
298928

2-[2-(5-Benzothieryl)ethoxy]-*N,N*-diethylethylamine oxalate



C16 H23 N O S . C2 H2 O4; Mol wt: 367.4635

ACTION – Agent for the treatment of neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, Huntington’s chorea and neuropathies that exhibits antihypoxic, neuroprotective and nerve regeneration-promoting effects. *In vitro*, compound gave 58% inhibition of human neutrophil elastase (HNE)-induced rat cortical neuronal cell death at a concentration of 0.1 µM. *In vivo*, it exhibited antihypoxic effects in mice at 100 mg/kg p.o. and was shown to stimulate the regeneration of sciatic nerve in a rat model of sciatic nerve crush injury at 10 mg/kg/day b.i.d. i.p. x 5 days. A representative compound from a series of *N*-alkoxyalkyl-*N,N*-dialkylamine derivatives, wherein the following are also included:



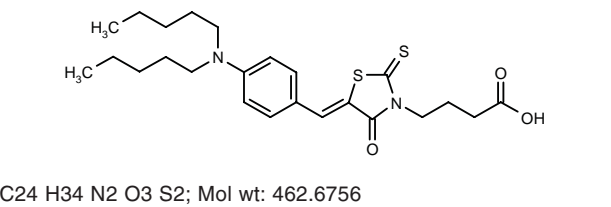
SOURCE – Toyama.

REFERENCES

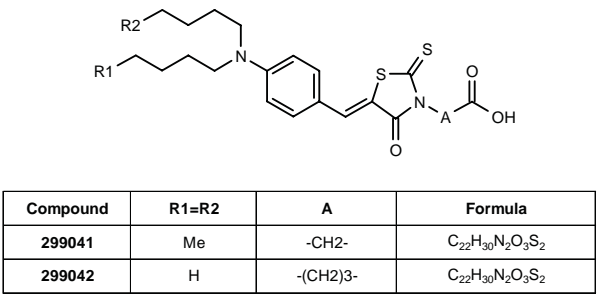
1. Ono, S. et al. (Toyama Chemical Co., Ltd.) *N*-Alkoxyalkyl-*N,N*-dialkylamine derivs. or salts thereof, and remedies for nerve degeneration diseases containing the same. WO 0076957.

299040

4-[(*Z*)-5-[4-(Dipentylamino)benzylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]butyric acid



ACTION – Agent for the treatment of Alzheimer’s disease, an inhibitor of amyloid protein aggregation also reported to be useful for imaging amyloid deposits. *In vitro*, compound was found to be active in several assays of amyloid inhibition, giving IC₅₀ values of 1.8-5 µM. Other exemplified compounds from this series of rhodanine derivatives include the following:



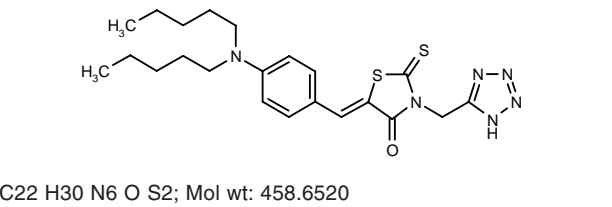
SOURCES – Pfizer; Yamanouchi.

REFERENCES

1. Augelli-Szafran, C.E. et al. (Pfizer Inc.;Yamanouchi Pharmaceutical Co., Ltd.) *Rhodanine derivs. for use in a method of inhibiting amyloid protein aggregation and imaging amyloid deposits.* WO 0076987.

299043

(*Z*)-5-[4-(Dipentylamino)benzylidene]-3-(1*H*-tetrazol-5-ylmethyl)-2-thioxothiazolidin-4-one



ACTION – Agent for the treatment of Alzheimer’s disease, an inhibitor of amyloid protein aggregation also reported to be useful for imaging amyloid deposits. *In vitro*, compound was found to be active in several assays of amyloid inhibition, giving respective IC₅₀ values of 1-10 µM.

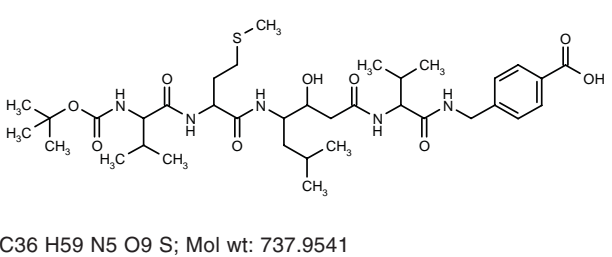
SOURCE – Pfizer.

REFERENCES

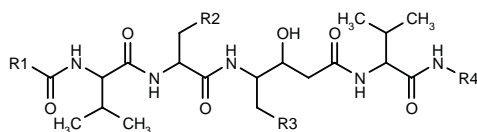
1. Augelli-Szafran, C.E. et al. (Pfizer Inc.) *Rhodanine derivs. and their use in inhibiting and imaging amyloids.* WO 0076988.

299088

4-(*tert*-Butoxycarbonyl-DL-valyl-DL-methionyl-DL-statinyL-DL-valylaminomethyl)benzoic acid



ACTION – Statine-derived tetrapeptide that inhibits the enzyme β-secretase (IC₅₀ < 10 µM). The inhibition of β-secretase reduces the production of amyloid β peptide from amyloid precursor protein and, consequently, the formation of amyloid plaques. Therefore, this compound is potentially useful for the treatment or prevention of Alzheimer’s disease. Other exemplified tetrapeptides include the following:



Compound	R1	R2	R3	R4	Formula
299090	t-BuO	CH ₂ SMe	i-Pr	3-(CO ₂ HCH ₂ O)-PhCH ₂	C ₃₇ H ₆₁ N ₅ O ₁₀ S
299091	t-BuO	CH ₂ SMe	i-Pr	3-CO ₂ H-PhCH ₂	C ₃₆ H ₅₉ N ₅ O ₉ S
299092	t-BuO	CH ₂ SMe	i-Pr	4-CO ₂ H-cyclohexyl	C ₃₅ H ₆₃ N ₅ O ₉ S
299098	t-BuO	CH ₂ SMe	i-Pr	3(S),5(S)-(CO ₂ H)2-cyclohexyl	C ₃₆ H ₆₃ N ₅ O ₁₁ S
299100	Me	Ph	Ph	4-CO ₂ H-PhCH ₂	C ₄₀ H ₅₁ N ₅ O ₈

SOURCE – Elan.

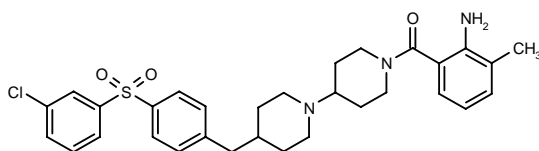
REFERENCES

1. John, V. et al. (Elan Pharmaceuticals, Inc.) *Statine-derived tetrapeptide inhibitors of beta-secretase*. WO 0077030.

SCH-211803

301636

2-[4-[4-(3-Chlorophenylsulfonyl)benzyl]-1,4'-bipiperidin-1'-ylcarbonyl]-6-methylphenylamine



C31 H36 Cl N3 O3 S; Mol wt: 566.1624

ACTION – Potent muscarinic M₂ receptor antagonist with 100-fold selectivity over other muscarinic receptors. Compound was active in animal models of cognition and showed a superior safety profile compared with cholinesterase inhibitors. It has advanced to phase I clinical trials for the treatment of Alzheimer's disease.

SOURCE – Schering-Plough.

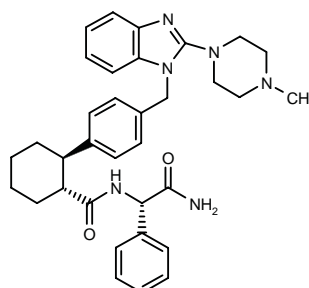
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1. Clader, J.W. et al. (Schering Corp.) *Muscarinic antagonists*. WO 0121590.
2. Asberom, T. et al. *Discovery of SCH 211803: A potent and highly selective muscarinic M₂ antagonist and a promising new approach to the treatment of Alzheimer's disease*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 169.

TREATMENT OF CEREbrovascular DISEASES

298209

(1*R*,2*R*)-*N*-[2-Amino-2-oxo-1(*S*)-phenylethyl]-2-[4-[2-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-1-ylmethyl]-phenyl]cyclohexanecarboxamide



C34 H40 N6 O2; Mol wt: 564.7300

ACTION – Agent for the treatment of ischemic brain diseases, an adenosine uptake inhibitor reported to possess good water solubility and therefore suitable for intravenous administration. *In vitro*, compound was shown to inhibit the binding of radiolabeled nitrobenzylthioinosin to calf cerebral cortex membrane preparations with a K_i value of about 2 nM, as well as to inhibit adenosine uptake in calf cortical synaptosomes with an IC₅₀ value of 14 nM. When tested *in vivo*, it produced a 91% reduction in infarct volume in a rat model of transient middle cerebral artery occlusion at 0.001 mg/kg/h i.v. and a 45% reduction in infarct volume in a rat model of subdural hematoma at a dose of 0.001 mg/kg/h i.v. A specifically claimed compound from a series of substituted phenylcyclohexane carboxylic acid derivatives.

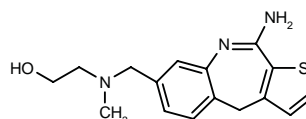
SOURCE – Bayer.

REFERENCES

1. Freund, W.-D. et al. (Bayer AG) *Subst. phenylcyclohexane carboxylic acid amides that have an adenosine uptake inhibiting effect*. DE 19924818, WO 0073275.

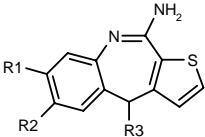
298301

2-[*N*-(10-Amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-ylmethyl)-*N*-methylamino]ethanol

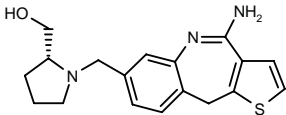


C16 H19 N3 O S; Mol wt: 301.4121

ACTION – Nitric oxide synthase (NOS) inhibitor exhibiting good selectivity for the neuronal and inducible isoforms compared to the endothelial isoform, potentially useful in the treatment or prophylaxis of hypoxia, stroke, ischemia, neurodegenerative disorders such as Parkinson’s disease, schizophrenia, anxiety, pain, migraine and inflammation. Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	R3	Formula
298302	H	H	SCH2CH2OH	C ₁₄ H ₁₄ N ₂ OS ₂
298303	CH2SCH2CH2OH	H	H	C ₁₅ H ₁₆ N ₂ OS ₂
298304	CH2SCH2CH2NH2	H	H	C ₁₅ H ₁₇ N ₃ S ₂
298305	2(R)-(CH2OH)- -1-pyrrolidinyl-CH2	H	H	C ₁₈ H ₂₁ N ₃ OS
298306	H	CH2NH(CH2)3OH	H	C ₁₆ H ₁₉ N ₃ OS
298307	CH2N(Me)- CH2C(Me)2OH	H	H	C ₁₈ H ₂₃ N ₃ OS
298308	H	2(S)-(CH2OH)- -1-pyrrolidinyl-CH2	H	C ₁₈ H ₂₁ N ₃ OS



298309: C18 H21 N3 O S

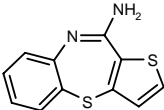
SOURCE – AstraZeneca.

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1. Matz, J. et al. (AstraZeneca AB) *Compounds*. WO 0073312.

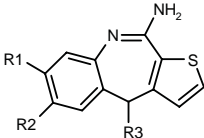
298310

Thieno[3,2-*b*][1,5]benzothiazepin-10-amine



C11 H8 N2 S2; Mol wt: 232.3302

ACTION – Nitric oxide synthase (NOS) inhibitor exhibiting good selectivity for the neuronal and inducible isoforms compared to the endothelial isoform, potentially useful in the treatment or prophylaxis of hypoxia, stroke, ischemia, neurodegenerative disorders such as Parkinson’s disease, schizophrenia, anxiety, pain, migraine and inflammation. Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	R3	Formula
298311	3-thienyl-C(=NH)NH	H	H	C ₁₇ H ₁₄ N ₄ S ₂
298312	Ac	H	H	C ₁₄ H ₁₂ N ₂ OS
298313	H	H	OH	C ₁₂ H ₁₀ N ₂ OS
298314	CH2Cl	H	H	C ₁₃ H ₁₁ ClN ₂ S
298315	H	i-PrOCO	H	C ₁₆ H ₁₆ N ₂ O ₂ S
298316	4-(2-Pyr)-1-Piz-CH2	H	H	C ₂₂ H ₂₃ N ₅ S
298317	H	4-MeO-Ph- CH2NHCH2	H	C ₂₁ H ₂₁ N ₃ OS
298318	CH2N(Me)- CH2CONH2	H	H	C ₁₆ H ₁₈ N ₄ OS

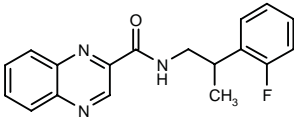
SOURCE – AstraZeneca.

REFERENCES

1. Matz, J. et al. (AstraZeneca AB) *New tricyclic amidine derivs. as inhibitors of nitric oxide synthase*. WO 0073313.

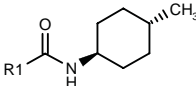
298335

N-[2-(2-Fluorophenyl)propyl]quinoxaline-2-carboxamide

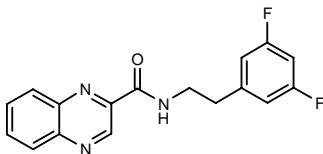


C18 H16 F N3 O; Mol wt: 309.3424

ACTION – Group I metabotropic glutamate receptor (mGluR) antagonist, potentially useful for inhibiting glutamate-induced neuronal damage, as well as for the treatment of neurological disorders such as senile dementia, Parkinson’s disease, Alzheimer’s disease, Huntington’s chorea, pain, epilepsy, head trauma, anoxic and ischemic injuries and tinnitus, pyschiatric disorders such as schizophrenia, depression and anxiety, and ophthalmological disorders such as diabetic retinopathies and glaucoma. Other specifically claimed compounds include the following:



Compound	R1	Formula
298340	2-PhO-3-Pyr	C ₁₉ H ₂₂ N ₂ O ₂
298341	2-benzofuryl	C ₁₆ H ₁₃ NO ₂
298342	6-MeO-3-quinolyl	C ₁₈ H ₂₂ N ₂ O ₂
298343	7-CF3-3-quinolyl	C ₁₈ H ₁₉ F ₃ N ₂ O



298345: C17 H13 F2 N3 O

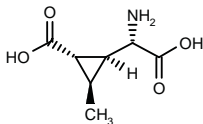
SOURCE – NPS Pharmaceuticals.

REFERENCES

1. Van Wagenen, B.C. et al. (NPS Pharmaceuticals, Inc.) *Metabotropic glutamate receptor antagonists and their use for treating central nervous system diseases*. WO 0073283.

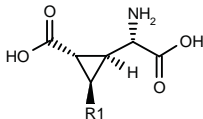
298669

(1'S,2'R,3'R)-2(S)-Amino-2-(2-carboxy-3-methyl-cyclopropyl)acetic acid



C7 H11 N O4; Mol wt: 173.1669

ACTION – Potent metabotropic glutamate receptor agonist, as demonstrated by a K_i value of 100.2 nM against [3 H]-LY-341495 binding to human mGluR₂ receptors. Potentially useful for the treatment of CNS disorders such as neurological diseases, e.g., neurodegenerative diseases, and drug withdrawal, and as an antipsychotic, anxiolytic, antidepressant, anticonvulsant, analgesic and antiemetic agent. Other specifically claimed compounds from this series of substituted cyclopropane derivatives are:



Compound	R1	Formula
298670	Et	C ₈ H ₁₃ NO ₄
298671	Pr	C ₉ H ₁₅ NO ₄
298672	vinyl	C ₈ H ₁₁ NO ₄
298673	CH ₂ CH ₂ Ph	C ₁₄ H ₁₇ NO ₄

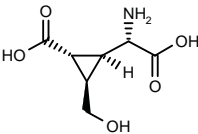
SOURCE – Lilly.

REFERENCES

1. Collado Cano, I. et al. (Lilly SA) *Excitatory amino acid receptor modulators*. WO 0075102.

298676

(1'S,2'R,3'R)-2(S)-Amino-2-[2-carboxy-3-(hydroxymethyl)cyclopropyl]acetic acid



C7 H11 N O5; Mol wt: 189.1659

ACTION – Potent metabotropic glutamate receptor agonist, as demonstrated by K_i values of 30.5 nM and 5.1 nM, respectively, against [3 H]-LY-341495 binding to human mGluR₂ and mGluR₃ subtypes. Potentially useful for the treatment of CNS disorders such as neurological diseases, e.g., neurodegenerative diseases, and drug withdrawal, and as an antipsychotic, anxiolytic, antidepressant, anticonvulsant, analgesic and antiemetic agent.

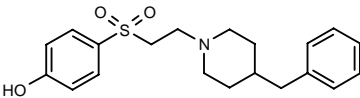
SOURCE – Lilly.

REFERENCES

1. Collado Cano, I. et al. (Lilly SA) *Excitatory amino acid receptor modulators*. WO 0075101.

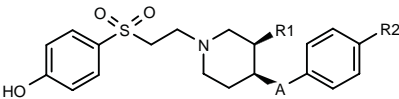
298791

4-[2-(4-Benzylpiperidin-1-yl)ethylsulfonyl]phenol



C20 H25 N O3 S; Mol wt: 359.4875

ACTION – Subtype-selective NMDA receptor blocker shown to inhibit [3 H]-Ro-25-6981 binding in rat brain membrane preparations (IC_{50} = 0.018 μ M), indicating antagonist activity at the NR2B subunit of the NMDA receptor. It was also effective in reducing NMDA-induced convulsions in mice with an ED_{50} of 1.1 mg/kg i.v. Potentially useful for the treatment of acute neurodegenerative disorders such as stroke and brain trauma, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Other specifically claimed ethanesulfonylpiperidine derivatives are:



Compound	R1	R2	A	Isomer	Formula
298792	H	Me	O		C ₂₀ H ₂₅ NO ₄ S
298793	OH	H	CH ₂	(-)-cis	C ₂₀ H ₂₅ NO ₄ S
298794	OH	H	CH ₂	(+)-cis	C ₂₀ H ₂₅ NO ₄ S
298795	OH	H	CH ₂	cis	C ₂₀ H ₂₅ NO ₄ S
298796	OH	Me	CH ₂	(-)-cis	C ₂₁ H ₂₇ NO ₄ S
298797	OH	Me	CH ₂	(+)-cis	C ₂₁ H ₂₇ NO ₄ S
298798	OH	Me	CH ₂	cis	C ₂₁ H ₂₇ NO ₄ S

SOURCE – Roche.

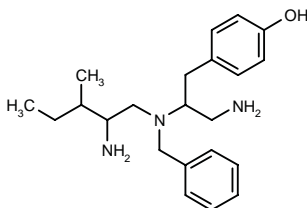
REFERENCES

1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *Ethanesulfonyl-piperidine derivs.* WO 0075109.

NBTA

301009

4-[3-Amino-2-[N-(2-amino-3-methylpentyl)-N-benzyl-amino]propyl]phenol



C22 H33 N3 O; Mol wt: 355.5227

ACTION – Neuroprotective agent, a potent and selective NMDA receptor open channel blocker ($IC_{50} = 80$ nM against recombinant NMDA receptors expressed in *Xenopus* oocytes) devoid of activity against GluR1 (AMPA) receptors at up to 1 μ M. In an *in vitro* model of NMDA-induced excitotoxicity in cultured rat hippocampal neurons, compound at 10 μ M protected neurons from NMDA receptor-mediated death (83% protection) with a potency comparable to memantine and MK-801 (93 and 89% protection, respectively, at 10 μ M). The neuroprotective effect of compound is specific for NMDA-mediated neurotoxicity because, unlike memantine and MK-801, it did not protect against kainate-induced neurotoxicity. Compound, which is expected to cross the blood–brain barrier, appears to be a useful lead for drug development.

SOURCES – University of California, San Diego, La Jolla, CA (US); Torrey Pines Institute for Molecular Studies, San Diego, CA (US).

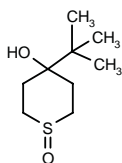
REFERENCES

1. Tai, W.-K. et al. A *N*-methyl-D-aspartate receptor channel blocker with neuroprotective activity. *Proc Natl Acad Sci USA* 2001, 98(6): 3519.

NV-31

300531

4-*tert*-Butyltetrahydro-2*H*-thiopyran-4-ol 1-oxide



C9 H18 O2 S; Mol wt: 190.3052

ACTION – Neuroprotective agent, a bilobalide derivative proven to concentration-dependently (1-100 nM) protect chick embryo neuronal cultures from apoptosis induced by serum deprivation and staurosporine exposure, and to reduce the percentage of apoptotic neurons in mixed cultures of neurons and astrocytes from neonatal rat hippocampus exposed to staurosporine. In this model, compound (10 and 100 nM) also significantly reduced cellular reactive oxygen species increased after serum deprivation and exposure to staurosporine, whereas at higher concentrations (1 μ M and above) it produced a nonspecific toxic effect. In an *in vivo* model of focal cerebral ischemia in mice, compound significantly reduced infarct area when given at a dose of 10 mg/kg i.p. 60 min before ischemia or 20 mg/kg i.p. immediately after ischemia.

SOURCES – Philipps-Universität Marburg, Marburg (DE); Schwabe.

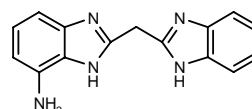
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SNX-912

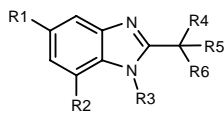
298575

2-(1*H*-Benzimidazol-2-ylmethyl)-1*H*-benzimidazol-7-amine



C15 H13 N5; Mol wt: 263.3027

ACTION – Apoptotic cell death inhibitor, particularly useful for the treatment or prevention of diseases that are associated with cell death such as stroke, ischemia, myocardial damage, neurodegeneration, trauma, autoimmune responses or inflammation. SNX-912 protected retinal ganglion cells from apoptotic cell death ($EC_{50} = 0.4$ nM) and was effective in reducing ischemic damage in oxygen/glucose-deprived cardiac myocytes. This compound reduced infarct area in rats subjected to middle cerebral artery occlusion, exhibiting 32 and 55% protection in terms of ischemic and infarct volume, respectively, at 25 mg/kg i.v. and 47 and 76% protection, respectively, at 5 mg/kg i.c.v. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
SNX-1018 [298576]	H	H	H	H	H	5-Me-4,5-dihydro-2-imidazolyl	C ₁₂ H ₁₄ N ₄
SNX-1771 [298577]	H	H	Me	Me	H	1-Me-4,5-dihydro-2-imidazolyl	C ₁₄ H ₁₈ N ₄
SNX-923 [298578]	H	NH2	H	H	H	5-Cl-2-benzimidazolyl	C ₁₅ H ₁₂ ClN ₅
SNX-947 [298579]	Cl	NH2	H	H	H	2-benzimidazolyl	C ₁₅ H ₁₂ ClN ₅
SNX-940 [298580]	H	NH2	H	H	H	4-F-2-benzimidazolyl	C ₁₅ H ₁₂ FN ₅
SNX-942 [298581]	H	NH2	H	H	H	5-F-2-benzimidazolyl	C ₁₅ H ₁₂ FN ₅
SNX-977 [298582]	H	NH2	H	H	H	5-CO2H-2-benzimidazolyl	C ₁₆ H ₁₃ N ₅ O ₂
SNX-944 [298583]	H	NH2	H	H	H	4-Me-2-benzimidazolyl	C ₁₆ H ₁₅ N ₅
SNX-1772 [298584]	H	H	H	-O-		2-indolyl	C ₁₆ H ₁₁ N ₃ O
SNX-1719 [298585]	H	H	H	-O-		2-benzimidazolyl	C ₁₅ H ₁₀ N ₄ O
SNX-980 [298586]	H	H	H	H	H	1,3-(Me)2-2-imidazolidinyl	C ₁₃ H ₁₈ N ₄

SOURCE – Elan.

REFERENCES

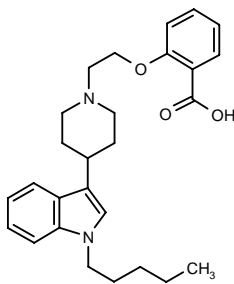
1. Bitler, C.M. et al. (Elan Corporation, plc) *Compsns. and methods for inhibiting cell death*. WO 0075117.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

298661

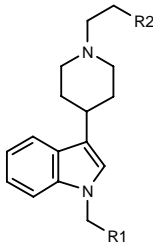
2-[2-[4-(1-Pentyl-1*H*-indol-3-yl)piperidin-1-yl]ethoxy]-benzoic acid



C27 H34 N2 O3; Mol wt: 434.5766

ACTION – Antihistaminic and antiallergic agent with reduced sedative and cardiovascular side effects. Antihistaminic activity was demonstrated *in vitro* by an IC₅₀ value of 57 nM against [³H]-mepyramine binding using guinea pig cerebellum membranes compared to IC₅₀ values of 226 and 214 nM for cetirizine and fexofenadine, respectively. *In vivo*, it demonstrated > 50% inhibition of histamine-induced wheal in rats at a dose of 3 mg/kg p.o. 4 h after administration, compared to 36 and 21% inhibition for cetirizine and fexofenadine,

respectively. In addition, compound is reported to display little or no penetration of the blood–brain barrier and to have little or no effects on blood pressure or heart rate at doses of 3-30 mg/kg p.o. in conscious spontaneously hypertensive rats. A representative compound from a series of indolylpiperidine derivatives, wherein the following compounds are also included:



Compound	R1	R2	Formula
298662	CH2OEt	4-(CO2HCH=CH)-Ph	C ₂₈ H ₃₄ N ₂ O ₃
298663	cyclopropyl	4-(CO2HCH2)-PhOCH2	C ₂₈ H ₃₄ N ₂ O ₃

SOURCE – Almirall Prodesfarma.

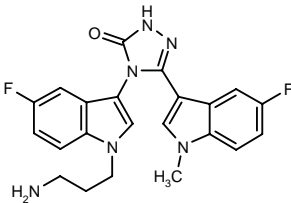
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ASTHMA THERAPY

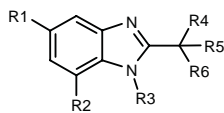
298027

4-[1-(3-Aminopropyl)-5-fluoro-1*H*-indol-3-yl]-5-(5-fluoro-1-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-1,2,4-triazol-3-one



C22 H20 F2 N6 O; Mol wt: 422.4370

ACTION – Protein kinase inhibitor, particularly active against protein kinase C, potentially useful for the treatment of inflammatory, immunologic, bronchopulmonary, cardiovascular, oncologic and neurodegenerative disorders. It has the advantage of being more soluble and less colored than previously known protein kinase C inhibitors. Other exemplified triazole derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
SNX-1018 [298576]	H	H	H	H	H	5-Me-4,5-dihydro-2-imidazolyl	C ₁₂ H ₁₄ N ₄
SNX-1771 [298577]	H	H	Me	Me	H	1-Me-4,5-dihydro-2-imidazolyl	C ₁₄ H ₁₈ N ₄
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SNX-940 [298580]	H	NH2	H	H	H	4-F-2-benzimidazolyl	C ₁₅ H ₁₂ FN ₅
SNX-942 [298581]	H	NH2	H	H	H	5-F-2-benzimidazolyl	C ₁₅ H ₁₂ FN ₅
SNX-977 [298582]	H	NH2	H	H	H	5-CO2H-2-benzimidazolyl	C ₁₆ H ₁₃ N ₅ O ₂
SNX-944 [298583]	H	NH2	H	H	H	4-Me-2-benzimidazolyl	C ₁₆ H ₁₅ N ₅
SNX-1772 [298584]	H	H	H	-O-		2-indolyl	C ₁₆ H ₁₁ N ₃ O
SNX-1719 [298585]	H	H	H	-O-		2-benzimidazolyl	C ₁₅ H ₁₀ N ₄ O
SNX-980 [298586]	H	H	H	H	H	1,3-(Me)2-2-imidazolidinyl	C ₁₃ H ₁₈ N ₄

SOURCE – Elan.

REFERENCES

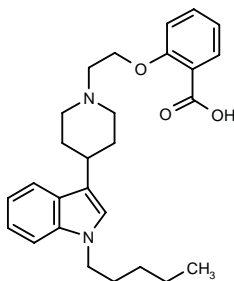
1. Bitler, C.M. et al. (Elan Corporation, plc) *Compsns. and methods for inhibiting cell death*. WO 0075117.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

298661

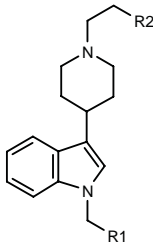
2-[2-[4-(1-Pentyl-1*H*-indol-3-yl)piperidin-1-yl]ethoxy]-benzoic acid



C27 H34 N2 O3; Mol wt: 434.5766

ACTION – Antihistaminic and antiallergic agent with reduced sedative and cardiovascular side effects. Antihistaminic activity was demonstrated *in vitro* by an IC₅₀ value of 57 nM against [³H]-mepyramine binding using guinea pig cerebellum membranes compared to IC₅₀ values of 226 and 214 nM for cetirizine and fexofenadine, respectively. *In vivo*, it demonstrated > 50% inhibition of histamine-induced wheal in rats at a dose of 3 mg/kg p.o. 4 h after administration, compared to 36 and 21% inhibition for cetirizine and fexofenadine,

respectively. In addition, compound is reported to display little or no penetration of the blood–brain barrier and to have little or no effects on blood pressure or heart rate at doses of 3-30 mg/kg p.o. in conscious spontaneously hypertensive rats. A representative compound from a series of indolylpiperidine derivatives, wherein the following compounds are also included:



Compound	R1	R2	Formula
298662	CH2OEt	4-(CO2HCH=CH)-Ph	C ₂₈ H ₃₄ N ₂ O ₃
298663	cyclopropyl	4-(CO2HCH2)-PhOCH2	C ₂₈ H ₃₄ N ₂ O ₃

SOURCE – Almirall Prodesfarma.

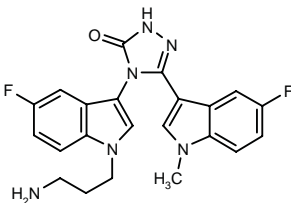
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1. Pages Santacana, L. et al. (Almirall Prodesfarma, SA) *Indolylpiperidine derivs. as antihistaminic and antiallergic agents*. WO 0075130.

ASTHMA THERAPY

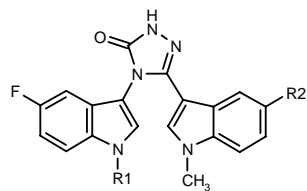
298027

4-[1-(3-Aminopropyl)-5-fluoro-1*H*-indol-3-yl]-5-(5-fluoro-1-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-1,2,4-triazol-3-one

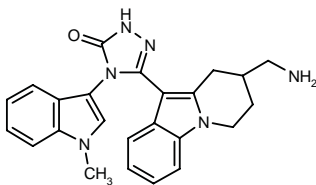


C22 H20 F2 N6 O; Mol wt: 422.4370

ACTION – Protein kinase inhibitor, particularly active against protein kinase C, potentially useful for the treatment of inflammatory, immunologic, bronchopulmonary, cardiovascular, oncologic and neurodegenerative disorders. It has the advantage of being more soluble and less colored than previously known protein kinase C inhibitors. Other exemplified triazole derivatives are:



Compound	R1	R2	Formula
298029	CH2CH2CH(Me)N(Me)2	F	C ₂₅ H ₂₆ F ₂ N ₆ O
298031	4-morpholinyl-(CH2)3	F	C ₂₆ H ₂₆ F ₂ N ₆ O ₂
298033	(CH2)3C(=NH)NH2	F	C ₂₃ H ₂₁ F ₂ N ₇ O
298034	3(R)-NH2-cyclopentyl	F	C ₂₄ H ₂₂ F ₂ N ₆ O
298035	(1S,3S)-3-NH2-cyclopentyl	F	C ₂₆ H ₂₆ F ₂ N ₆ O
298036	(1S,3R)-3-(NH2CH2)-cyclopentyl	F	C ₂₅ H ₂₄ F ₂ N ₆ O
298037	1-Me-4-Pip	F	C ₂₅ H ₂₄ F ₂ N ₆ O
298038	(CH2)3NH2	Me	C ₂₃ H ₂₃ FN ₆ O
298039	(CH2)3NH2	OMe	C ₂₃ H ₂₃ FN ₆ O ₂



298040: C24 H24 N6 O

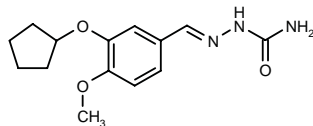
SOURCE – AstraZeneca.

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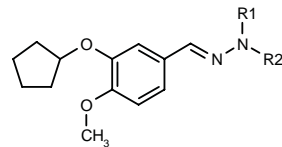
298240

(E)-3-(Cyclopentyloxy)-4-methoxybenzaldehyde semi-carbazone



C14 H19 N3 O3; Mol wt: 277.3221

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4; 66.2% inhibition of enzyme partially purified from human U937 cells at 2 μM vs. 62.5% inhibition for rolipram at the same concentration) and TNF, with potential in the treatment or prevention of asthma, arthritis, bronchitis, psoriasis, allergic rhinitis, dermatitis, AIDS, Crohn’s disease, septic shock and cachexia. Other exemplified compounds from this series of catechol hydrazone derivatives include the following:



Compound	R1	R2	Formula
298243	4-Pyr-CO	H	C ₁₉ H ₂₁ N ₃ O ₃
298244	CO2Et	H	C ₁₆ H ₂₂ N ₂ O ₄
298245	Ph	H	C ₁₉ H ₂₂ N ₂ O ₂
298247	Ac	H	C ₁₅ H ₂₀ N ₂ O ₃
298248	7-Cl-4-quinolyl	H	C ₂₂ H ₂₂ ClN ₃ O ₂
298250	4,5-dihydro-2-imidazolyl	H	C ₁₆ H ₂₂ N ₄ O ₂
298251	CSNH2	H	C ₁₄ H ₁₉ N ₃ O ₂ S
298252	4-Cl-Ph	H	C ₁₉ H ₂₁ ClN ₂ O ₂
298254	COCH2N(Me)3 ⁺ Cl ⁻	H	C ₁₈ H ₂₈ ClN ₃ O ₃
298255	-(CH2)5-		C ₁₈ H ₂₆ N ₂ O ₂
298257	-CH2CH2OCH2CH2-		C ₁₇ H ₂₄ N ₂ O ₃
298259	C(=NH)NH2	H	C ₁₄ H ₂₀ N ₄ O ₂
298260	2-Pyr	H	C ₁₈ H ₂₁ N ₃ O ₂
298262	2-CO2H-Ph	H	C ₂₀ H ₂₂ N ₂ O ₄

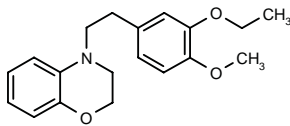
SOURCE – Cheil Jedang.

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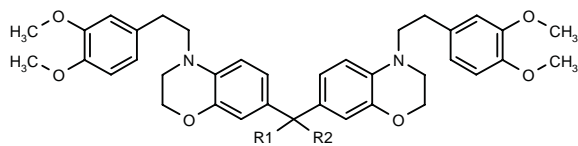
298416

4-[2-(3-Ethoxy-4-methoxyphenyl)ethyl]-3,4-dihydro-2H-1,4-benzoxazine



C19 H23 N O3; Mol wt: 313.3947

ACTION – Antiasthmatic agent, an inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.26 ± 0.01 μM against enzyme from U937 cells). *In vivo*, compound gave 51% inhibition of antigen-induced bronchoconstriction in sensitized guinea pigs at 40 mg/kg i.v. Other compounds from this series of 2,3-dihydro-1,4-benzoxazine derivatives include the following:



Compound	R1	R2	Formula
298417	-O-		C ₃₇ H ₄₀ N ₂ O ₇
298418	H	H	C ₃₇ H ₄₂ N ₂ O ₆
298419	H	OH	C ₃₇ H ₄₂ N ₂ O ₇

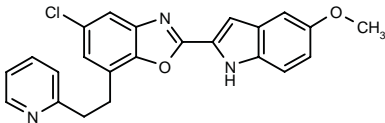
SOURCE – Fuji Photo Film.

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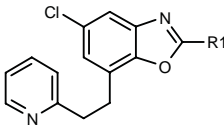
298475

5-Chloro-2-(5-methoxy-1*H*-indol-2-yl)-7-[2-(2-pyridinyl)-ethyl]benzoxazole



C23 H18 Cl N3 O2; Mol wt: 403.8672

ACTION – Antiasthmatic agent, an inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.16 μM against enzyme from bovine tracheal smooth muscle vs. 3.7 μM for rolipram). Other compounds from this series of 2-heteroaryl and 2-heterocyclic benzoxazoles include the following:



Compound	R1	Formula
298477	2-furyl	C ₁₈ H ₁₃ ClN ₂ O ₂
298478	3-thienyl	C ₁₈ H ₁₃ ClN ₂ OS
298479	2-benzothieryl	C ₂₂ H ₁₅ ClN ₂ OS
298480	5-benzotriazolyl	C ₂₀ H ₁₄ ClN ₅ O
298481	2,4-(Me)2-3-furyl	C ₂₀ H ₁₇ ClN ₂ O ₂

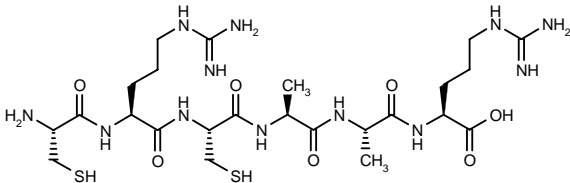
SOURCE – Euroceltique.

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1. Cavalla, D.J. et al. (Euroceltique SA) *2-Heteroaryl and 2-heterocyclic benzoxazoles as PDE IV inhibitors for the treatment of asthma.* US 6166041.

298518

L-Cysteinyl-L-arginyl-L-cysteinyl-L-alanyl-L-alanyl-L-arginine



C24 H46 N12 O7 S2; Mol wt: 678.8364

ACTION – A representative compound from a series of hexapeptides that inhibit the binding of β-chemokines such as eotaxin, eotaxin-2, MCP-3, MCP-5 and RANTES to the chemokine CCR3 receptor and are therefore potentially useful in the treatment of diseases associated with aberrant leukocyte recruitment and/or activation including arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, allergies, asthma and AIDS-related inflammatory disorders. *In vitro*, compound inhibited the binding of [¹²⁵I]-eotaxin to CCR3 in human eosinophils, as well as eotaxin-induced calcium mobilization in human eosinophils, with IC₅₀ values of about 40 μM. It further inhibited eotaxin-induced chemotaxis of human eosinophils with an IC₅₀ value of about 20 μM. Selectivity for the CCR3 receptor was demonstrated in binding assays using 293 cells transfected with CCR3, CXCR4, CXCR2 and CCR2 receptors, where it was shown to specifically inhibit [¹²⁵I]-eotaxin binding to CCR3 but not to CCR2, CXCR2 or CXCR4.

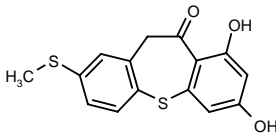
SOURCE – CellTek Biotechnologies.

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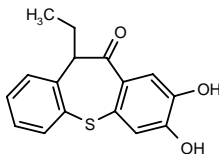
298563

7,9-Dihydroxy-2-(methylsulfanyl)dibenzo[*b,f*]thiepin-10(11*H*)-one



C15 H12 O3 S2; Mol wt: 304.3888

ACTION – Antiasthmatic agent reported to act by relaxing tracheal smooth muscle, suppressing respiratory tract hypersensitivity and inhibiting inflammatory cell infiltration into the respiratory tract. *In vitro*, compound was shown to produce a complete relaxation of K⁺-contracted guinea pig tracheal smooth muscle preparations at 10 μM. In addition, it inhibited ovalbumin-induced immediate and late asthmatic reactions in sensitized guinea pigs by 70 and 77%, respectively, at a dose of 10 mg/kg p.o. and was shown to inhibit infiltration of inflammatory cells into the bronchoalveolar fluid (BAL) in these animals. No signs of toxicity were observed following administration of up to 500 mg/kg/day p.o. x 2 weeks to rats. Another tricyclic fused heterocyclic compound is:



298564: C16 H14 O3 S

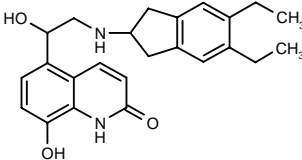
SOURCE – Nippon Suisan.

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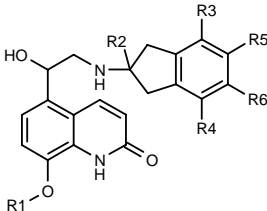
298713

5-[2-(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-ylamino)-1-hydroxyethyl]-8-hydroxyquinolin-2(1*H*)-one



C24 H28 N2 O3; Mol wt: 392.4962

ACTION – Potent and selective β_2 -adrenoceptor agonist with a long duration of action, potentially useful for the treat-ment of obstructive or inflammatory airways diseases such as asthma. Compound was tested in a guinea pig tracheal strip assay, where it exhibited a T(50%) value (i.e., time for inhibition of contraction to decay to 50% of its maximum value) of > 400 min at 71 nM. Other exemplified bicyclic compounds include the following:



Compound	R1	R2	R3=R4	R5	R6	Isomer	Formula
298714	H	H	Et	H	H		C ₂₄ H ₂₈ N ₂ O ₃
298715	H	H	H	-(CH2)4-			C ₂₄ H ₂₆ N ₂ O ₃
298719	CH2Ph	Me	H	H	H	R	C ₂₈ H ₂₈ N ₂ O ₃
298720	H	Me	H	-(CH2)4-		R	C ₂₅ H ₂₈ N ₂ O ₃

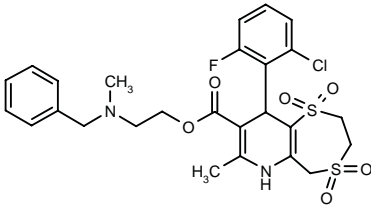
SOURCE – Novartis.

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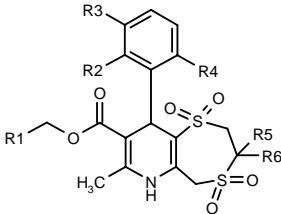
299044

9-(2-Chloro-6-fluorophenyl)-7-methyl-2,3,6,9-tetrahydro-5*H*-[1,4]dithiepino[6,5-*b*]pyridine-8-carboxylic acid 2-(*N*-benzyl-*N*-methylamino)ethyl ester 1,1,4,4-tetraoxide isomer A



C26 H28 Cl F N2 O6 S2; Mol wt: 583.0982

ACTION – Calcium channel antagonist (IC₅₀ = 43 nM against [³H]-nitrendipine binding in rabbit heart preparations) proven to inhibit KCl-induced contractions of dog tracheal rings with an IC₅₀ value of 0.66 μ M. Potentially useful in the treatment or prevention of hypersensitivity, allergy, asthma, bronchospasm, dysmenorrhea, esophageal spasm, glaucoma, preterm labor, urinary tract disorders, gastrointestinal motility disorders and cardiovascular disorders. Other compounds from this series of dithiepino[6,5-*b*]pyridines include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
299045	H	F	CF3	H	-CH2-		C ₁₉ H ₁₇ F ₄ NO ₆ S ₂
299046	CH2N(Me)CH2Ph	H	NO2	H	H	H	C ₂₆ H ₂₉ N ₃ O ₆ S ₂
299047	CH2N(Me)CH2Ph	F	H	CF3	H	H	C ₂₇ H ₂₈ F ₄ N ₂ O ₆ S ₂
299048	CH2N(Me)CH2Ph	F	CF3	H	H	H	C ₂₇ H ₂₈ F ₄ N ₂ O ₆ S ₂

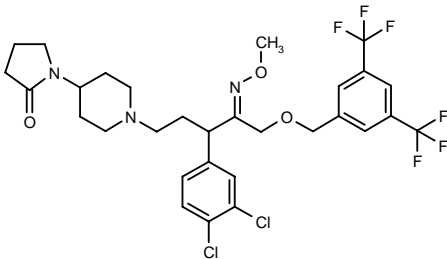
SOURCE – Ortho-McNeil.

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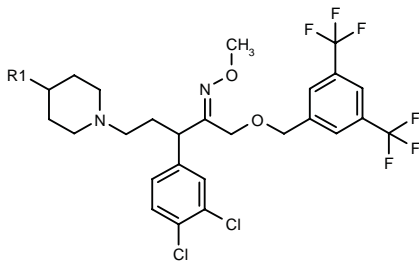
300448

1-[1-[5-[3,5-Bis(trifluoromethyl)benzyloxy]-3-(3,4-dichlorophenyl)-4(*Z*)-(methoxyimino)pentyl]piperidin-4-yl]pyrrolidin-2-one



C30 H33 Cl2 F6 N3 O3; Mol wt: 668.5027

ACTION – Dual tachykinin NK₁/NK₂ antagonist with nanomolar affinity for both human NK₁ and NK₂ receptors expressed in CHO cells (K_i = 9 and 7 nM, respectively) and potentially useful for the treatment of asthma. Other related piperidines include the following:



Compound	R1	Formula
300443	3-(NH ₂ CO)-1-Pip	C ₃₂ H ₃₈ Cl ₂ F ₆ N ₄ O ₃
300447	-L-Pro-NH ₂	C ₃₁ H ₃₆ Cl ₂ F ₆ N ₄ O ₃
300450	2-oxo-1-Pip-CH ₂	C ₃₂ H ₃₇ Cl ₂ F ₆ N ₃ O ₃
300451	2-(HOCH ₂ CH ₂)-1-Pip-CH ₂	C ₃₄ H ₄₃ Cl ₂ F ₆ N ₃ O ₃

SOURCE – Schering-Plough.

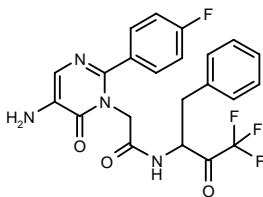
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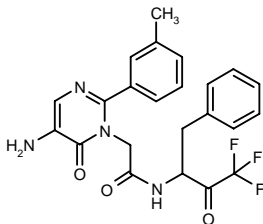
300676

2-[5-Amino-2-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidin-1-yl]-N-(1-benzyl-3,3,3-trifluoro-2-oxopropyl)-acetamide



C22 H18 F4 N4 O3; Mol wt: 462.4012

ACTION – Nonpeptide human chymase inhibitor (K_i = 0.305 μM) possessing a good oral pharmacokinetic profile in rats: it is rapidly absorbed following oral administration, with a C_{max} of 2.59 μM and an oral bioavailability of 14.5%. Potentially useful as a tool to elucidate the pathophysiological role of chymase and as a potential therapeutic agent for chymase-related diseases such as allergic inflammatory diseases. Another compound with high selectivity for chymase is:



300677: C23 H21 F3 N4 O3

SOURCE – Welfide.

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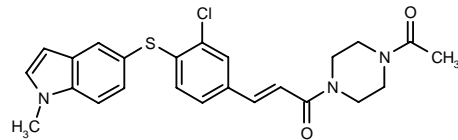
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A-295339

301572

5-[4-[3-(4-Acetylpiperazin-1-yl)-3-oxo-1-propenyl]-2-chlorophenylsulfanyl]-1-methyl-1H-indole



C24 H24 Cl N3 O2 S; Mol wt: 453.9916

ACTION – Cell adhesion inhibitor, a small, water-soluble ligand that selectively binds to the I domain allosteric site (IDAS) of the adhesion molecule LFA-1, potentially useful for the treatment of inflammatory and immune diseases.

SOURCE – Abbott.

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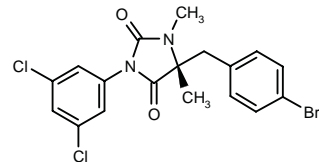
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BIRT-377

294649

5(R)-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione

BIRT-0377



C18 H15 Br Cl2 N2 O2; Mol wt: 442.1385

ACTION – Cell adhesion inhibitor, an orally bioavailable small molecule that specifically interacts with LFA-1 via noncovalent binding to the CD11a chain and prevents binding of LFA-1 to its ligand ICAM-1 ($K_d = 25.8$ nM), as well as LFA-1-mediated SKW3 cell binding to immobilized ICAM-1 ($IC_{50} = 2.6$ μ M). Compound inhibits lymphocyte activity both *in vitro* and *in vivo*: it blocked the LFA-1-dependent production of IL-2 by human peripheral blood lymphocytes stimulated with superantigen (staphylococcal enterotoxin B [SEB]; $IC_{50} = 0.85$ μ M) and inhibited SEB-induced IL-2 production in mice at doses of 25 and 50 mg/kg p.o. Potentially useful for the treatment of immunological disorders.

SOURCE – Boehringer Ingelheim.

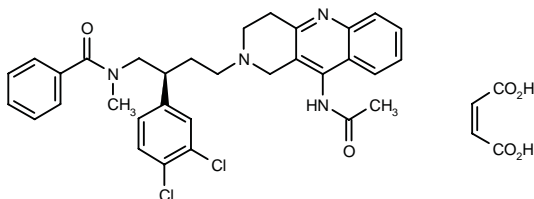
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NK-5807*

273498

(–)-N-[4-(10-Acetamido-1,2,3,4-tetrahydrobenzo[b]-[1,6]naphthyridin-2-yl)-2-(S)-(3,4-dichlorophenyl)butyl]-N-methylbenzamide maleate



C32 H32 Cl2 N4 O2 . C4 H4 O4; Mol wt: 691.6084

ACTION – Tachykinin NK₂ receptor antagonist proven to inhibit bronchoconstriction induced by acetylcholine or ovalbumin in sensitized guinea pigs at an oral dose of 20 mg/kg. At higher doses (40 and 80 mg/kg) it inhibited plasma extravasation in distal airways induced by electrical stimulation of the vagus nerve and was also able to inhibit capsaicin-induced cough at doses of 5 mg/kg or more. Potentially useful for the treatment of asthma.

SOURCE – Nippon Kayaku.

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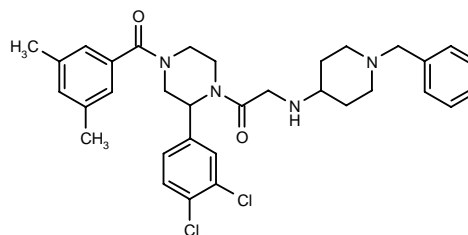
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*Identified compound **273498** Drug Data Rep 1999, 021(05): 0404.

SCH-62373

301770

1-Benzyl-N-[2-[2-(3,4-dichlorophenyl)-4-(3,5-dimethylbenzoyl)piperazin-1-yl]-2-oxoethyl]piperidin-4-amine



C33 H38 Cl2 N4 O2; Mol wt: 593.5952

ACTION – Dual neurokinin NK₁/NK₂ receptor antagonist ($IC_{50} = 1.8$ and 4.9 nM, respectively for human NK₁ and NK₂ receptors) with a pA₂ of 6.5 for functional antagonism in isolated guinea pig vas deferens (NK₁ receptors) or isolated hamster trachea (NK₂ receptors). Potentially useful for the treatment of allergic inflammatory diseases such as asthma.

SOURCE – Schering-Plough.

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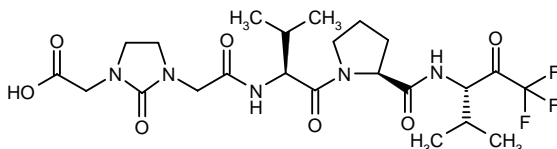
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AGENTS FOR RESPIRATORY DISTRESS SYNDROME

AE-3763*

294800

1-[N-[2-[3-(Carboxymethyl)-2-oxoimidazolidin-1-yl]acetyl]-L-valyl-L-prolinamide N-[3,3,3-trifluoro-1(S)-isopropyl-2-oxopropyl]amide



C23 H34 F3 N5 O7; Mol wt: 549.5436

ACTION – Potent and selective inhibitor of human neutrophil elastase (HNE; $K_i = 3.2$ nM) proven to attenuate lung hemorrhage induced by tracheal instillation of HNE in hamsters with an ED_{50} of 0.42 mg/kg/h by 70-min infusion and an ED_{50} of 1.25 mg/kg by i.v. bolus injection. In this model, compound also inhibited the infiltration of white blood cells to bronchoalveolar lavage fluid (BALF), an effect which was closely related to inhibition of elastase activity in BALF. In acute liver injury induced by systemic administration of lipopolysaccharide (LPS) and D-galactosamine in rats, compound given as an i.v. bolus injection followed by infusion caused a dose-dependent reduction in elastase activity and hepatic enzyme activity in plasma. In addition, compound given as repeated doses of 100 mg/kg i.p. 2-h intervals, significantly increased the survival rate in D-galactosamine-sensitized LPS-shocked mice. Potentially useful for the treatment of acute degenerative diseases associated with excess elastases such as acute respiratory distress syndrome (ARDS) and septic shock.

SOURCE – Dainippon Pharmaceutical.

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3. Kuromiya, A. et al. *AE-3763, a novel inhibitor of human neutrophil elastase (2): Effects of AE-3763 on acute organ failure models*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-559.

4. Okazaki, H. et al. *Pharmacological effects of AE-3763, a novel elastase inhibitor*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-031.

5. Omodani, T. et al. *Novel peptidyl trifluoromethyl ketone inhibitor of human neutrophil elastase*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 243.

6. Shiratake, R. et al. *Synthesis and structure-activity relationship of a novel elastase inhibitor AE-3763 and related compounds*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-030.

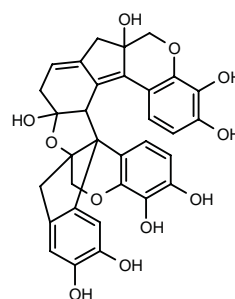
*Identified compound **294800** Drug Data Rep 2001, 023(02): 0136.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

297921

8,10-Dihydro-16e,6a-([1,2]benzenomethano)-6H-[1]benzopyrano[3'',4'':4',5']cyclopenta[1',2':4,5]benzofuro[2,3-c][1]benzopyran-3,4,7a,10a,13,14,20,21(11H,16dH)-octaol



C32 H26 O11; Mol wt: 586.5464

ACTION – Antihypertensive compound isolated from an aqueous extract of the heartwood of *Caesalpinia brasiliensis* (Palo de Brazil). This compound demonstrated activity in hypertensive Sprague-Dawley rats, reducing systolic blood pressure about 35% and bringing it into normal range when the extracted fraction that contains this compound was administered at a concentration of 100 µg/ml to the drinking water of animals.

SOURCE – Brigham Young University, Provo, UT (US).

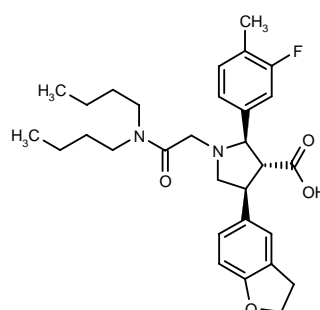
REFERENCES

1. Owen, N.L. and Wood, S.G. (Brigham Young University) *Antihypertensive cpd. from Caesalpinia brasiliensis*. WO 0071115.

A-292438

301573

1-[2-(Dibutylamino)-2-oxoethyl]-4(S)-(2,3-dihydro-benzofuran-5-yl)-2(R)-(3-fluoro-4-methylphenyl)pyrrolidine-3(R)-carboxylic acid



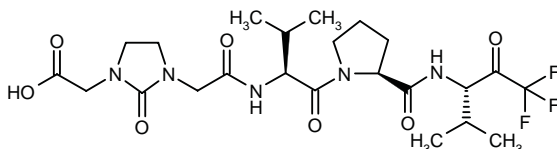
C30 H39 F N2 O4; Mol wt: 510.6461

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

AE-3763*

294800

1-[N-[2-[3-(Carboxymethyl)-2-oxoimidazolidin-1-yl]acetyl]-L-valyl-L-prolinamide N-[3,3,3-trifluoro-1(S)-isopropyl-2-oxopropyl]amide



C23 H34 F3 N5 O7; Mol wt: 549.5436

ACTION – Potent and selective inhibitor of human neutrophil elastase (HNE; $K_i = 3.2$ nM) proven to attenuate lung hemorrhage induced by tracheal instillation of HNE in hamsters with an ED_{50} of 0.42 mg/kg/h by 70-min infusion and an ED_{50} of 1.25 mg/kg by i.v. bolus injection. In this model, compound also inhibited the infiltration of white blood cells to bronchoalveolar lavage fluid (BALF), an effect which was closely related to inhibition of elastase activity in BALF. In acute liver injury induced by systemic administration of lipopolysaccharide (LPS) and D-galactosamine in rats, compound given as an i.v. bolus injection followed by infusion caused a dose-dependent reduction in elastase activity and hepatic enzyme activity in plasma. In addition, compound given as repeated doses of 100 mg/kg i.p. 2-h intervals, significantly increased the survival rate in D-galactosamine-sensitized LPS-shocked mice. Potentially useful for the treatment of acute degenerative diseases associated with excess elastases such as acute respiratory distress syndrome (ARDS) and septic shock.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Sato, F. et al. (Dainippon Pharmaceutical Co., Ltd.) *Heterocyclic cpds., intermediates thereof and elastase inhibitors*. JP 2000256396, WO 0052032.

2. Kubo, T. et al. *AE-3763, a novel inhibitor of human neutrophil elastase (1): Biochemical and pharmacological properties of AE-3763*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-558.

3. Kuromiya, A. et al. *AE-3763, a novel inhibitor of human neutrophil elastase (2): Effects of AE-3763 on acute organ failure models*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-559.

4. Okazaki, H. et al. *Pharmacological effects of AE-3763, a novel elastase inhibitor*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-031.

5. Omodani, T. et al. *Novel peptidyl trifluoromethyl ketone inhibitor of human neutrophil elastase*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 243.

6. Shiratake, R. et al. *Synthesis and structure-activity relationship of a novel elastase inhibitor AE-3763 and related compounds*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-030.

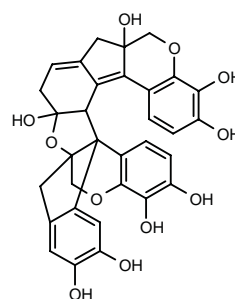
*Identified compound **294800** Drug Data Rep 2001, 023(02): 0136.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

297921

8,10-Dihydro-16e,6a-([1,2]benzenomethano)-6H-[1]benzopyrano[3'',4'':4',5']cyclopenta[1',2':4,5]benzofuro[2,3-c][1]benzopyran-3,4,7a,10a,13,14,20,21(11H,16dH)-octaol



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ACTION – Antihypertensive compound isolated from an aqueous extract of the heartwood of *Caesalpinia brasiliensis* (Palo de Brazil). This compound demonstrated activity in hypertensive Sprague-Dawley rats, reducing systolic blood pressure about 35% and bringing it into normal range when the extracted fraction that contains this compound was administered at a concentration of 100 µg/ml to the drinking water of animals.

SOURCE – Brigham Young University, Provo, UT (US).

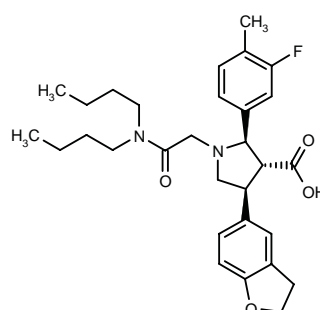
REFERENCES

1. Owen, N.L. and Wood, S.G. (Brigham Young University) *Antihypertensive cpd. from Caesalpinia brasiliensis*. WO 0071115.

A-292438

301573

1-[2-(Dibutylamino)-2-oxoethyl]-4(S)-(2,3-dihydro-benzofuran-5-yl)-2(R)-(3-fluoro-4-methylphenyl)pyrrolidine-3(R)-carboxylic acid



C30 H39 F N2 O4; Mol wt: 510.6461

ACTION – Oral available, metabolically stable selective endothelin ET_A receptor antagonist derived from ABT-627.

SOURCE – Abbott.

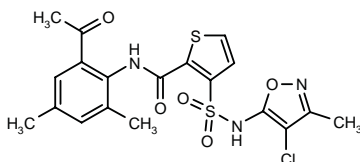
REFERENCES

1. Jae, H.-S. et al. *Promising ETA selective antagonist after ABT-627/ABT-546*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 57.

TBC-3214

281452

N-(2-Acetyl-4,6-dimethylphenyl)-3-[*N*-(4-chloro-3-methylisoxazol-5-yl)sulfamoyl]thiophene-2-carboxamide



C19 H18 Cl N3 O5 S2; Mol wt: 467.9522

ACTION – Endothelin ET_A receptor antagonist, a thiophene sulfonamide with extremely high potency (IC₅₀ = 40 pM) and selectivity (400,000-fold) for ETA versus ET_B receptors. Compound showed a serum-half life of > 4 h after oral administration and an oral bioavailability of 25% in rats, 42% in cats and 70% in dogs. TBC-3214 has demonstrated efficacy in rat and newborn piglet models of hypoxia-induced pulmonary hypertension. Potentially useful for the treatment of congestive heart failure and pulmonary hypertension.

SOURCE – Texas Biotechnology.

REFERENCES

1. Wu, C. et al. (Texas Biotechnology Corp.) *Sulfonamides for treatment of endothelin-mediated disorders*. EP 0980369, US 5783705, WO 9849162.
2. Decker, E.R. et al. *Evaluation of novel, highly selective ET_A receptor antagonists in hypoxia-induced pulmonary hypertension*. 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst 189.
3. Wu, C. et al. *Acyl substitution at the ortho position of anilides enhances oral bioavailability of thiophene sulfonamides: TBC3214, and ET_A selective endothelin antagonist*. J Med Chem 2001, 44(8): 1211.
4. Wu, C. et al. *Discovery of potent, orally available, ET_A selective endothelin antagonists: TBC3214 and TBC3711*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst ORGN 233.
5. Wu, C. et al. *Discovery of potent, orally available, ET_A selective endothelin antagonists: TBC3214 and TBC3711*. 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst 022.

TELMISARTAN/HYDROCHLOROTHIAZIDE

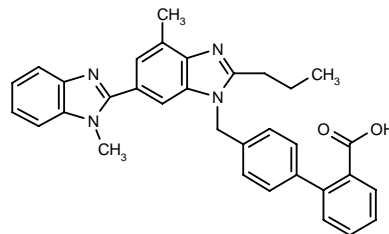
296815

Fixed-dose combination of telmisartan and hydrochlorothiazide

Telmisartan

195173

4'-[4-Methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid

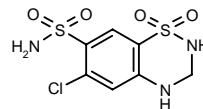


C33 H30 N4 O2; Mol wt: 514.6330

Hydrochlorothiazide

115231

6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide



C7 H8 Cl N3 O4 S2; Mol wt: 297.7422

ACTION – Combination of the orally active angiotensin II (AT₁) antagonist telmisartan and the diuretic hydrochlorothiazide.

INDICATION – Second-line treatment of hypertension.

PRESENTATION – Tablets containing telmisartan 40 and 80 mg and a fixed dose of 12.5 mg hydrochlorothiazide.

PROPRIETARY NAME – Micardis HCT (US).

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Lacourcière, Y. and Poirier, L. *Comparison of a fixed-dose combination of telmisartan 40 mg + hydrochlorothiazide 12.5 mg with telmisartan 40 mg in the control of mild-to-moderate hypertension*. J Renin-Angiotensin-Aldosterone Syst 2001, 2(1): Abst PC.31.
2. Lacourcière, Y. et al. *Comparison of the antihypertensive effects of a fixed-dose combination of telmisartan and hydrochlorothiazide versus telmisartan monotherapy in mild-to-moderate hypertension*. J Renin-Angiotensin-Aldosterone Syst 2001, 2(1): Abst PC.9.
3. Laws, D. *Safety and efficacy of long-term exposure to monotherapy or combination therapy with telmisartan*. J Renin-Angiotensin-Aldosterone Syst 2001, 2(1): Abst PC.35.
4. McGill, J.B. and Reilly, P.A. *Combination treatment with telmisartan and hydrochlorothiazide in black patients with mild to moderate hypertension*. Clin Cardiol 2001, 24(1): 66.
5. *Boehringer Ingelheim seeks approval for combination hypertension treatments*. DailyDrugNews.com (Daily Essentials) 2000, Feb 8.
6. *FDA approves Boehringer Ingelheim's Micardis HCT*. DailyDrugNews.com (Daily Essentials) 2000, Nov 21.
7. *Glaxo Wellcome, Boehringer Ingelheim collaborate to bring telmisartan market*. DailyDrugNews.com (Daily Essentials) 1998, March 16.

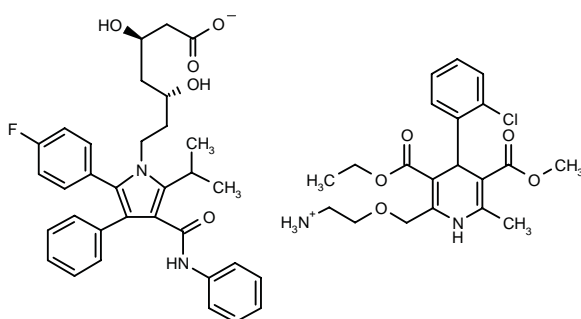
8. *Product development pipeline*. GlaxoSmithKline Product Pipeline 2001, February.

9. *Second-line antihypertensive combination therapy launched in U.S.* DailyDrugNews.com (Daily Essentials) 2001, April 6.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

298514

(3*R*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrol-1-yl]-3,5-dihydroxyheptanoic acid 2-[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-6-methyl-5-(methoxycarbonyl)-1,4-dihydropyridin-2-ylmethoxy]-ethanaminium salt



C33 H34 F N2 O5 . C20 H26 Cl N2 O5; Mol wt: 967.5260

ACTION – Mutual salt of amlodipine and atorvastatin, claimed for the treatment of atherosclerosis, angina pectoris and combined hypertension and hyperlipidemia, as well as for managing cardiac risk in subjects at risk of suffering an adverse cardiac event.

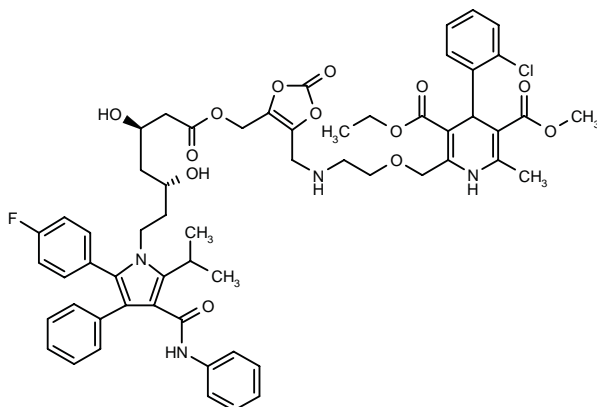
SOURCE – Pfizer.

REFERENCES

1. Chang, G. and Hamanaka, E.S. (Pfizer Products Inc.) *Mutual salt of amlodipine and atorvastatin*. WO 0073271.

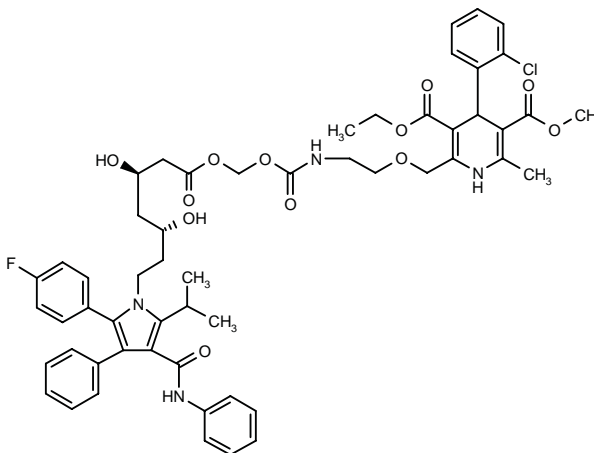
298515

4-(2-Chlorophenyl)-2-[2-[5-[(3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoyloxymethyl]-2-oxo-1,3-dioxol-4-ylmethylamino]ethoxymethyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl 5-methyl diester



C58 H62 Cl F N4 O13; Mol wt: 1077.5940

ACTION – Prodrug of amlodipine and atorvastatin, claimed for the treatment of atherosclerosis, angina pectoris and combined hypertension and hyperlipidemia, as well as for managing cardiac risk in subjects at risk of suffering an adverse cardiac event. Another specifically claimed compound from this series of mutual prodrugs of amlodipine and atorvastatin is:



298516: C55 H60 Cl F N4 O12

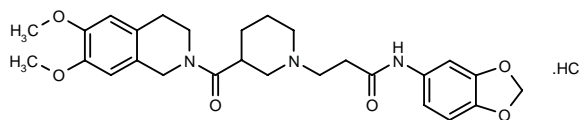
SOURCE – Pfizer.

REFERENCES

1. Chang, G. et al. (Pfizer Products Inc.) *Mutual prodrugs of amlodipine and atorvastatin*. WO 0073298.

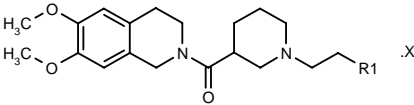
298566

N-(1,3-Benzodioxol-5-yl)-3-[3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl)piperidin-1-yl]-propionamide hydrochloride



C27 H33 N3 O6 . HCl; Mol wt: 532.0336

ACTION – Bradycardic agent that inhibits the I_f current and is reported to be devoid of serious side effects such as convulsions, potentially useful for the treatment or prevention of ischemic heart diseases such as precordial anxiety and myocardial infarction, and circulatory diseases such as congestive heart failure and arrhythmia. Compound was shown to reduce heart rate in guinea pig right atrium preparations with an EC_{30} value of 0.30 μ M. No spasms were observed following administration of 40 mg/kg i.v. of compound to rats. Other exemplified compounds from this series of isoquinoline derivatives include the following:



Compound	R1	Isomer	X	Formula
298568	4-MeO-PhNHCO		HCl	C ₂₇ H ₃₅ N ₃ O ₅ ·HCl
298569	1,3-benzodioxol-5-yl-NHCO	R	L-tartrate	C ₂₇ H ₃₃ N ₃ O ₆ ·C ₄ H ₆ O ₆
298571	1,3-benzodioxol-5-yl-NHCO	S	D-tartrate	C ₂₇ H ₃₃ N ₃ O ₆ ·C ₄ H ₆ O ₆
298573	1,3-benzodioxol-5-yl-CONH		HCl	C ₂₇ H ₃₃ N ₃ O ₆ ·HCl
298574	6-benzothiazolyl-NHCO		HCl	C ₂₇ H ₃₂ N ₄ O ₄ S·HCl

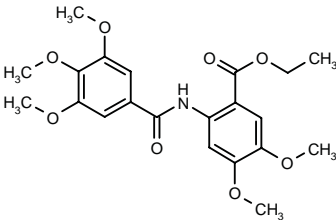
SOURCE – Yamanouchi.

REFERENCES

1. Watanabe, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel isoquinoline derivs. or salts thereof*. WO 0075133.

300469

4,5-Dimethoxy-2-(3,4,5-trimethoxybenzamido)benzoic acid ethyl ester



C21 H25 N O8; Mol wt: 419.4275

ACTION – Tranilast derivative proven to selectively inhibit the proliferation of smooth muscle cells (SMC) over endothelial cells (EC) derived from human coronary artery (IC₅₀ = 0.31 and 4.6 μM, respectively), being superior to tranilast as regards potency and cell selectivity (IC₅₀ = 24.5 and 19.1 μM against SMC and EC, respectively). Potentially useful for the treatment of restenosis.

SOURCE – Japan Energy.

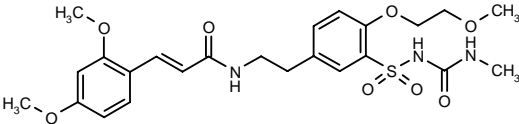
REFERENCES

1. Ogita, H. et al. *Synthesis and structure-activity relationship of diarylamide derivatives as selective inhibitors of the proliferation of human coronary artery smooth muscle cells*. Bioorg Med Chem Lett 2001, 11(4): 549.

ANTIARRHYTHMIC DRUGS

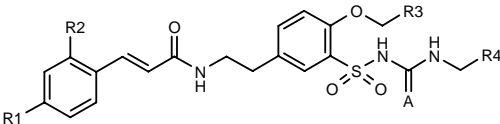
297964

3-(2,4-Dimethoxyphenyl)-N-[2-[4-(2-methoxyethoxy)-3-(3-methylureidosulfonyl)phenyl]ethyl]-2(E)-propenamide



C24 H31 N3 O8 S; Mol wt: 521.5879

ACTION – An inhibitor of ATP-sensitive potassium channels in the cardiac muscle and/or in the cardiac nerve with little or no hypoglycemic activity, potentially useful for the treatment of cardiovascular disorders such as coronary heart disease, arrhythmias, cardiac insufficiency and cardiomyopathies, for the prevention of sudden cardiac death and for improving decreased contractility of the heart. *In vitro*, compound was shown to inhibit rilmakalim-induced reductions in action potential duration in guinea pig papillary muscle, while *in vivo* it was shown to reduce chloroform-induced ventricular fibrillation in mice (60% fibrillation ratio at 3 mg/kg i.p. vs. 100% fibrillation ratio for control animals); the activity of the compound in this test was abolished by administration of atropine, thus indicating that it acts via a vagal mechanism of action. Other exemplified compounds from this series of cinnamoylaminoalkyl-substituted benzenesulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
297966	OMe	OMe	H	H	C ₂₂ H ₂₇ N ₃ O ₆ S ₂
297967	Me	Me	H	H	C ₂₂ H ₂₇ N ₃ O ₄ S ₂
297968	OMe	OMe	CH ₂ OMe	H	C ₂₄ H ₃₁ N ₃ O ₇ S ₂
297969	OMe	OMe	CH ₂ OMe	Me	C ₂₅ H ₃₃ N ₃ O ₇ S ₂
297970	H	H	H	H	C ₂₀ H ₂₃ N ₃ O ₄ S ₂

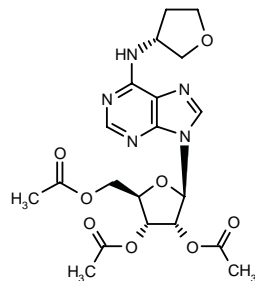
SOURCE – Aventis Pharma.

REFERENCES

1. Heitsch, H. et al. (Aventis Pharma Deutschland GmbH) *Cinnamoylaminoalkyl-substd. benzenesulfonamide derivs*. DE 19923086, WO 0071513.

298204

2,3,5-Tri-*O*-acetyl-*N*⁶-[3(*R*)-tetrahydrofuryl]adenosine



C20 H25 N5 O8; Mol wt: 463.4445

ACTION – Prodrug of the selective adenosine A₁ receptor agonist CVT-510⁺, found to exhibit rapid conversion to the parent compound following oral administration to rats and to produce a decrease in heart rate in these animals of about 100-150 bpm when administered at 0.5 mg/kg p.o., with a rapid onset of action; its effects were reversed by the administration of theophylline, showing that it acts via an interaction with adenosine receptors. Claimed to be useful for the treatment of coronary electrical disorders such as supraventricular tachycardias, atrial fibrillation, atrial flutter and AV nodal reentrant tachycardia.

SOURCE – CV Therapeutics.

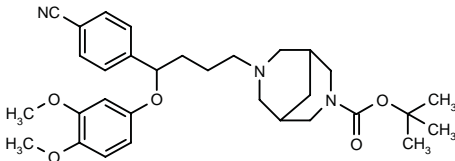
REFERENCES

1. Blackburn, B.K. et al. (CV Therapeutics, Inc.) *Orally active A1 adenosine receptor agonists*. WO 0071558.

⁺Drug Data Rep 1998, 020(06): 0498.

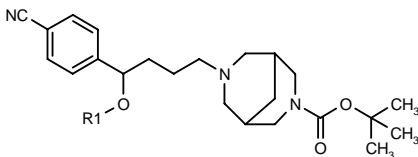
298834

7-[4-(4-Cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester



C31 H41 N3 O5; Mol wt: 535.6809

ACTION – Antiarrhythmic agent that exhibits myocardial electrophysiological activity, preferably class III activity, and is indicated for the treatment or prevention of arrhythmias, particularly atrial and ventricular arrhythmias. Other exemplified bispidine compounds are:



Compound	R1	Formula
298835	4-OH-Ph	C ₂₉ H ₃₇ N ₃ O ₄
298836	4-Pyr-CH2	C ₂₉ H ₃₈ N ₄ O ₃

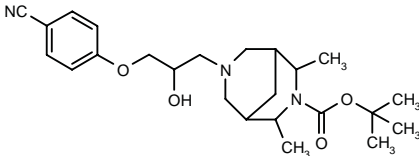
SOURCE – AstraZeneca.

REFERENCES

1. Frantsi, M. et al. (AstraZeneca AB) *New bispine cpds. useful in the treatment of cardiac arrhythmias*. WO 0076997.

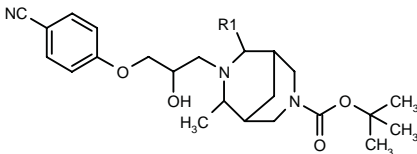
298837

7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester



C24 H35 N3 O4; Mol wt: 429.5575

ACTION – Antiarrhythmic agent that exhibits myocardial electrophysiological activity, preferably class III activity, and is indicated for the treatment or prevention of arrhythmias, particularly atrial and ventricular arrhythmias. Other exemplified bispidine compounds are:



Compound	R1	Isomer	Formula
298838	Me		C ₂₄ H ₃₅ N ₃ O ₄
298839	H		C ₂₃ H ₃₃ N ₃ O ₄
298840	Me	2S	C ₂₄ H ₃₅ N ₃ O ₄

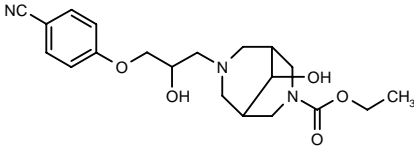
SOURCE – AstraZeneca.

REFERENCES

1. Björsne, M. et al. (AstraZeneca AB) *New bispidine cpds. useful in the treatment of cardiac arrhythmias*. WO 0076998.

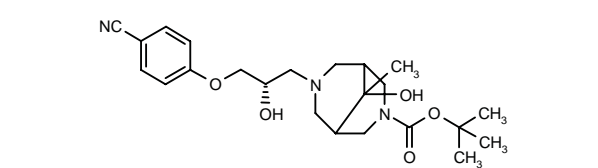
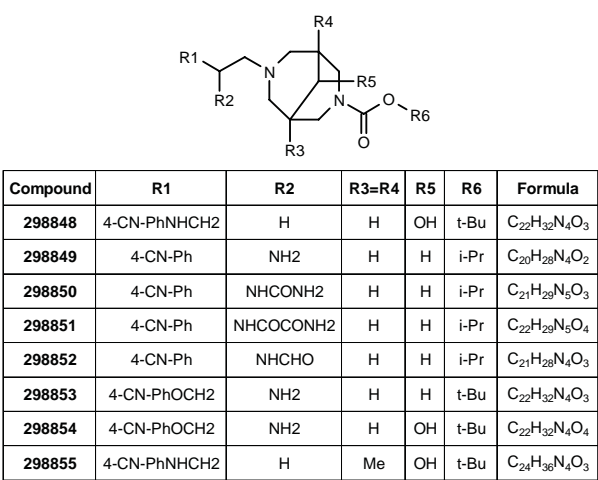
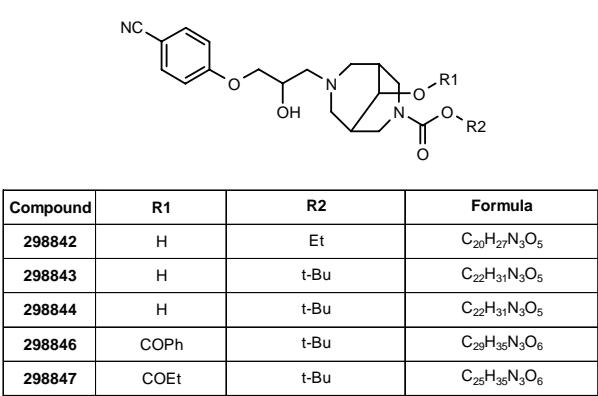
298841

7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-9-hydroxy-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester isomer A



C20 H27 N3 O5; Mol wt: 389.4493

ACTION – Antiarrhythmic agent that exhibits myocardial electrophysiological activity, preferably class III activity, and is indicated for the treatment or prevention of arrhythmias, particularly atrial and ventricular arrhythmias. Other exemplified bispidine compounds are:



298845: C23 H33 N3 O5

SOURCE – AstraZeneca.

REFERENCES

1. Björe, A. et al. (AstraZeneca AB) *New bispidine cpds. useful in the treatment of cardiac arrhythmias*. WO 0076999.

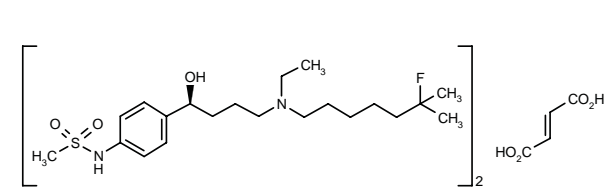
TRECETILIDE FUMARATE*

Prop INN; USAN

240450

(–)-N-[4-[4-[N-Ethyl-N-(6-fluoro-6-methylheptyl)amino]-1(S)-hydroxybutyl]phenyl]methanesulfonamide fumarate (2:1)

PNU-108342E



(C21 H37 F N2 O3 S2)2 . C4 H4 O4; Mol wt: 949.2682

ACTION – Class III antiarrhythmic agent, an ibutilide analogue that retains the ability to increase refractoriness of cardiac tissue at both slow and fast pacing rates (38.9 and 27.7% increase at 1 and 3 Hz, respectively, at 10 μM in rabbit papillary muscle) but shows improved metabolic stability and is devoid of proarrhythmic activity in rabbits. *In vivo*, it showed excellent activity in canine models of reentrant atrial flutter (AFL) and ventricular tachyarrhythmias at cumulative doses of 0.24-2.4 μmol/kg i.v. Currently undergoing clinical trials for the treatment of atrial arrhythmias.

SOURCE – Pharmacia.

REFERENCES

1. Hester, J.B. Jr. and Gibson, J.K. (Pharmacia Corp.) *Antiarrhythmic (S)-enantiomers of methanesulfonamides*. EP 0802900, JP 1999500418, WO 9621643.

2. Buist, S.C. et al. *Sensitive determination of a new antiarrhythmic agent, trecetilide, in plasma by high-performance liquid chromatography with fluorescence detection*. J Chromatogr 1998, 828(1-2): 259.

3. Hester, J.B. *Progress toward the development of a safe and effective agent for treating reentrant cardiac arrhythmias: Synthesis and evaluation of ibutilide analogues with enhanced metabolic stability and diminished proarrhythmic potential*. J Med Chem 2001, 44(7): 1099.

4. *Proposed international nonproprietary names (Prop. INN): List 79*. WHO Drug Inf 1998, 12(2): 113.

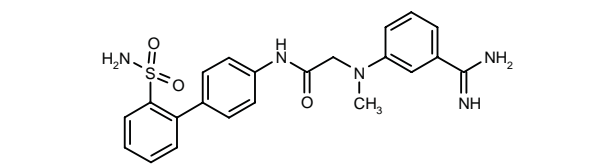
*Identified compound **240450** (see **239794**) Drug Data Rep 1996, 018(11): 0978.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

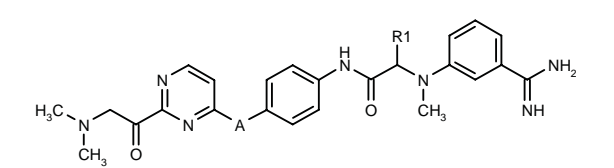
298168

N²-(3-Amidinophenyl)-N²-methyl-N¹-(2'-sulfamoyl-biphenyl-4-yl)glycinamide

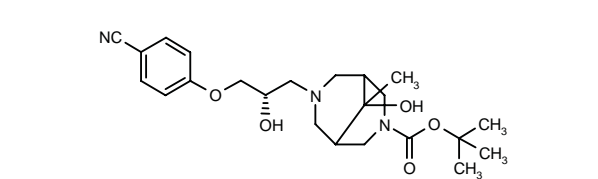
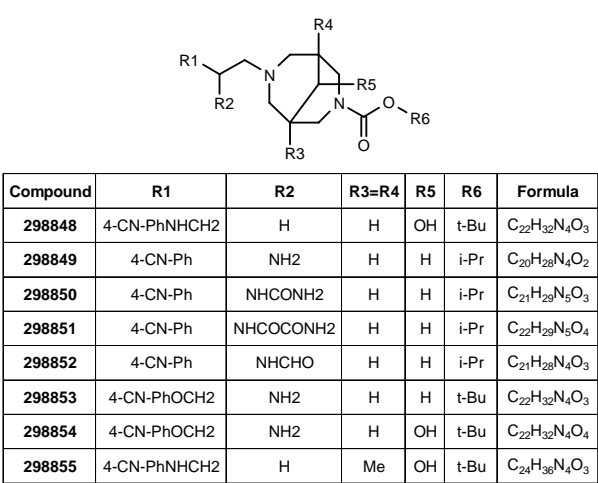
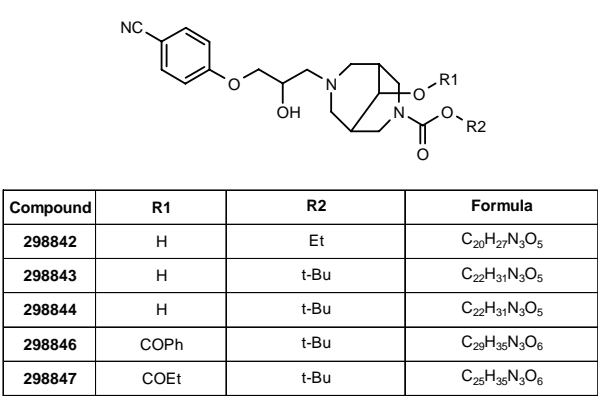


C22 H23 N5 O3 S; Mol wt: 437.5217

ACTION – Antithrombotic agent, a potent inhibitor of factor Xa with high selectivity for factor Xa versus other proteases of the coagulation or the fibrinolytic cascades such as thrombin. Other exemplified compounds are:



Compound	R1	A	Formula
298169	H	bond	C ₂₄ H ₂₇ N ₇ O ₂
298172	Ph	CH2	C ₃₁ H ₃₃ N ₇ O ₂



298845: C23 H33 N3 O5

SOURCE – AstraZeneca.

REFERENCES

1. Björe, A. et al. (AstraZeneca AB) *New bispidine cpds. useful in the treatment of cardiac arrhythmias*. WO 0076999.

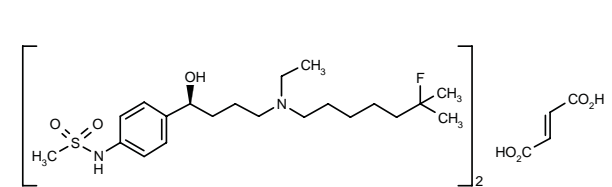
TRECETILIDE FUMARATE*

Prop INN; USAN

240450

(–)-N-[4-[4-[N-Ethyl-N-(6-fluoro-6-methylheptyl)amino]-1(S)-hydroxybutyl]phenyl]methanesulfonamide fumarate (2:1)

PNU-108342E



(C21 H37 F N2 O3 S2)2 . C4 H4 O4; Mol wt: 949.2682

ACTION – Class III antiarrhythmic agent, an ibutilide analogue that retains the ability to increase refractoriness of cardiac tissue at both slow and fast pacing rates (38.9 and 27.7% increase at 1 and 3 Hz, respectively, at 10 μM in rabbit papillary muscle) but shows improved metabolic stability and is devoid of proarrhythmic activity in rabbits. *In vivo*, it showed excellent activity in canine models of reentrant atrial flutter (AFL) and ventricular tachyarrhythmias at cumulative doses of 0.24-2.4 μmol/kg i.v. Currently undergoing clinical trials for the treatment of atrial arrhythmias.

SOURCE – Pharmacia.

REFERENCES

1. Hester, J.B. Jr. and Gibson, J.K. (Pharmacia Corp.) *Antiarrhythmic (S)-enantiomers of methanesulfonamides*. EP 0802900, JP 1999500418, WO 9621643.

2. Buist, S.C. et al. *Sensitive determination of a new antiarrhythmic agent, trecetilide, in plasma by high-performance liquid chromatography with fluorescence detection*. J Chromatogr 1998, 828(1-2): 259.

3. Hester, J.B. *Progress toward the development of a safe and effective agent for treating reentrant cardiac arrhythmias: Synthesis and evaluation of ibutilide analogues with enhanced metabolic stability and diminished proarrhythmic potential*. J Med Chem 2001, 44(7): 1099.

4. *Proposed international nonproprietary names (Prop. INN): List 79*. WHO Drug Inf 1998, 12(2): 113.

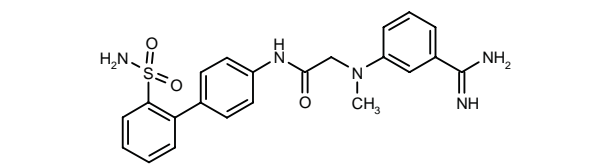
*Identified compound **240450** (see **239794**) Drug Data Rep 1996, 018(11): 0978.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

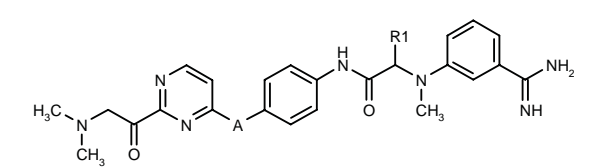
298168

N²-(3-Amidinophenyl)-N²-methyl-N¹-(2'-sulfamoyl-biphenyl-4-yl)glycinamide

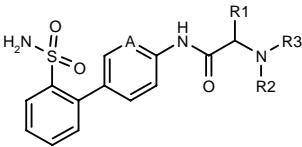


C22 H23 N5 O3 S; Mol wt: 437.5217

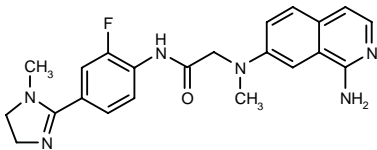
ACTION – Antithrombotic agent, a potent inhibitor of factor Xa with high selectivity for factor Xa versus other proteases of the coagulation or the fibrinolytic cascades such as thrombin. Other exemplified compounds are:



Compound	R1	A	Formula
298169	H	bond	C ₂₄ H ₂₇ N ₇ O ₂
298172	Ph	CH2	C ₃₁ H ₃₃ N ₇ O ₂



Compound	R1	R2	R3	A	Formula
298170	H	Me	1-NH2-7-isoquinolyl	CH	C ₂₄ H ₂₃ N ₅ O ₃ S
298171	Ph	Me	3-[NH2C(=NH)]-Ph	CH	C ₂₈ H ₂₇ N ₅ O ₃ S
298173	Ph	Me	3-[NH2C(=NH)]-Ph	N	C ₂₇ H ₂₆ N ₆ O ₃ S
298174	Ph	H	3-[NH2C(=NH)]-Ph	CH	C ₂₇ H ₂₅ N ₅ O ₃ S
298175	Ph	Me	2-OH-5-[NH2C(=NH)]Ph	CH	C ₂₈ H ₂₇ N ₅ O ₄ S
298177	-(CH2)3-		3-[NH2C(=NH)]-PhCO	CH	C ₂₅ H ₂₅ N ₅ O ₄ S
298178	NHAc	Me	3-[NH2C(=NH)]-Ph	CH	C ₂₅ H ₂₈ N ₆ O ₄ S



298176: C22 H23 F N6 O

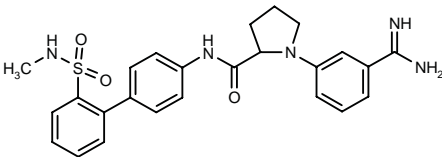
SOURCE – COR Therapeutics.

REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Inhibitors of factor Xa*. WO 0071493, WO 0071507.

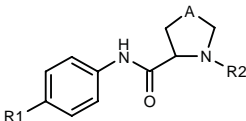
298179

1-(3-Amidinophenyl)-N-[2'-(N-methylsulfamoyl)biphenyl-4-yl]-DL-prolinamide



C25 H27 N5 O3 S; Mol wt: 477.5863

ACTION – Antithrombotic agent, a potent inhibitor of factor Xa with high selectivity for factor Xa versus other proteases of the coagulation or the fibrinolytic cascades such as thrombin. Other exemplified compounds include the following:



Compound	R1	R2	A	Formula
298180	2-CN-Ph	1-NH2-7-isoquinolyl	-CH2-	C ₂₇ H ₂₃ N ₅ O
298181	2-[N(Me)2CH2CO]-4-pyrimidinyl-CH2	3-[NH2C(=NH)]-Ph	-CH2-	C ₂₇ H ₃₁ N ₇ O ₂
298182	2-NH2-1-imidazolyl-CH2	1-NH2-7-isoquinolyl	-CH2-	C ₂₄ H ₂₅ N ₇ O
298183	6-(NH2CO)-4-pyrimidinyl-CO	3-[NH2C(=NH)]-Ph	-(CH2)2-	C ₂₅ H ₂₅ N ₇ O ₃
298184	2-NH2-1-imidazolyl-CO	1-NH2-7-isoquinolyl	-(CH2)2-	C ₂₅ H ₂₅ N ₇ O ₂
298185	2-(NH2SO2)-Ph	3-[NH2C(=NH)]-Ph	-(CH2)2-	C ₂₅ H ₂₇ N ₅ O ₃ S
298186	3-(NH2CH2)-4-Pyr	1-NH2-7-isoquinolyl	-(CH2)2-	C ₂₇ H ₂₈ N ₆ O
298187	2-(MeSO2)-Ph	3-[NH2C(=NH)]-Ph	-CH2-	C ₂₅ H ₂₆ N ₄ O ₃ S

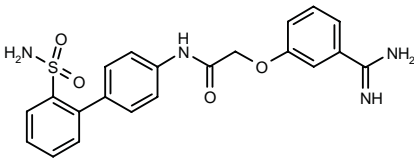
SOURCE – COR Therapeutics.

REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Inhibitors of factor Xa*. WO 0071515, WO 0071516.

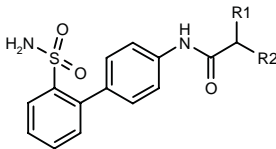
298188

2-(3-Amidinophenoxy)-N-(2'-sulfamoylbiphenyl-4-yl)-acetamide

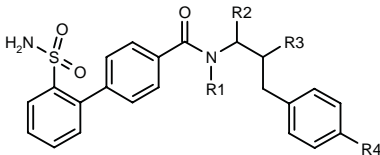


C21 H20 N4 O4 S; Mol wt: 424.4790

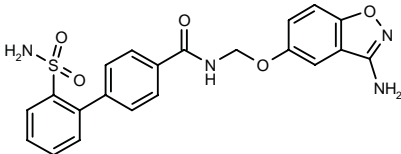
ACTION – Antithrombotic agent, a potent inhibitor of factor Xa with high selectivity for factor Xa versus other proteases of the coagulation or the fibrinolytic cascades such as thrombin. Other exemplified compounds include the following:



Compound	R1		R2	Formula
298189		2-imidazolyl-CH2	3-NH2-1,2-benz-isothiazol-5-yl-O	C ₂₅ H ₂₂ N ₆ O ₄ S ₂
298190		6-indazolyl-CH(3-MeO-PhCH2)O	CH2Ph	C ₃₇ H ₃₄ N ₄ O ₅ S
298191		3-NH2-1,2-benzisoxazol-5-yl-OCH(CH2Ph)	4-OH-Ph	C ₃₅ H ₃₀ N ₄ O ₆ S
298192		2-NH2-5-benzimidazolyl-SCH2	Me	C ₂₃ H ₂₃ N ₅ O ₃ S ₂



Compound	R1	R2	R3	R4	Formula
298193	4-Pyr-CH2	CH2Ph	3-[NH2C(=NH)]-PhO	H	C ₄₂ H ₃₉ N ₆ O ₄ S
298194	CH2Ph	CH2CH2-CON(Me)2	3-NH2-5-indazolyl-S	H	C ₄₁ H ₄₂ N ₆ O ₄ S ₂
298195	Me	CH2CH2-CO2Me	3-NH2-1,2-benz-isoxazol-5-yl-O	NH2	C ₃₄ H ₃₅ N ₅ O ₇ S



298196: C21 H18 N4 O5 S

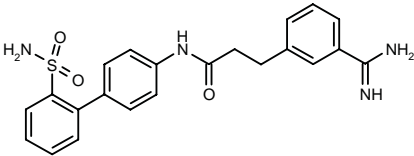
SOURCE – COR Therapeutics.

REFERENCES

1. Su, T. et al. (COR Therapeutics, Inc.) *Inhibitors of factor Xa*. WO 0071508, WO 0071510, WO 0071511.

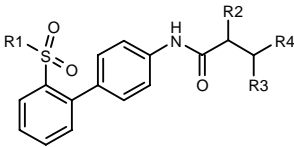
298197

3-(3-Amidinophenyl)-N-(2'-sulfamoylbiphenyl-4-yl)-propionamide



C22 H22 N4 O3 S; Mol wt: 422.5068

ACTION – Antithrombotic agent, a potent inhibitor of factor Xa with high selectivity for factor Xa versus other proteases of the coagulation or the fibrinolytic cascades such as thrombin. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
298198	Me	H	H	3-[NH2C(=NH)]-Ph	C ₂₃ H ₂₃ N ₃ O ₃ S
298199	NH2	H	H	2-(MeOCH2CH2O)-5-[NH2C(=NH)]-Ph	C ₂₅ H ₂₈ N ₄ O ₅ S
298200	NH2	H	CF3	3-[NH2C(=NH)]-Ph	C ₂₃ H ₂₁ F ₃ N ₄ O ₃ S
298201	NH2	F	Me	3-[NH2C(=NH)]-Ph	C ₂₃ H ₂₃ FN ₄ O ₃ S
298202	NH2	Me	H	3-[NH2C(=NH)]-Ph	C ₂₃ H ₂₄ N ₄ O ₃ S
298203	NH2	Ph	H	1-NH2-7-isoquinolyl	C ₃₀ H ₂₆ N ₄ O ₃ S

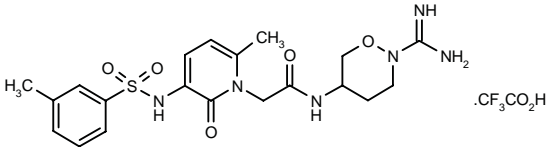
SOURCE – COR Therapeutics.

REFERENCES

1. Song, Y. et al. (COR Therapeutics, Inc.) *Inhibitors of factor Xa*. WO 0071509, WO 0071512.

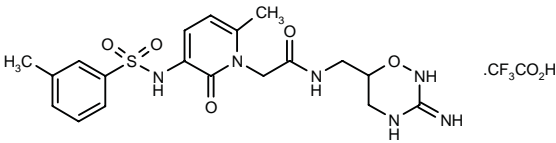
298214

N-(2-Amidinotetrahydro-2H-1,2-oxazin-5-yl)-2-[6-methyl-3-(3-methylphenylsulfonamido)-2-oxo-1,2-dihydropyridin-1-yl]acetamide trifluoroacetate



C20 H26 N6 O5 S . C2 H F3 O2; Mol wt: 576.5503

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of thrombin (K_i = 0.38 nM). Another specifically claimed compound from this series of oxazaheterocycles is:



298215: C19 H24 N6 O5 S . C2 H F3 O2

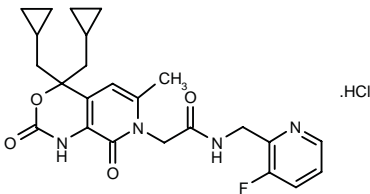
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Wang, A. et al. (3-Dimensional Pharmaceuticals, Inc.) *Oxazaheterocycles as protease inhibitors*. WO 0073302.

298609

2-[4,4-Bis(cyclopropylmethyl)-6-methyl-2,8-dioxo-2,4,7,8-tetrahydro-1H-pyrido[3,4-d][1,3]oxazin-7-yl]-N-(3-fluoropyridin-2-ylmethyl)acetamide hydrochloride



C24 H27 F N4 O4 . HCl; Mol wt: 490.9602

ACTION – Anticoagulant, a thrombin inhibitor that is potentially useful for the treatment and prevention of thrombotic conditions, particularly coronary artery and cerebrovascular diseases.

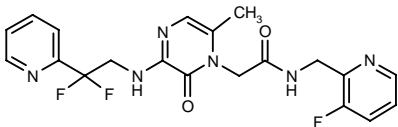
SOURCE – Merck & Co.

REFERENCES

1. Coburn, C.A. and Burgey, C.S. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0074682.

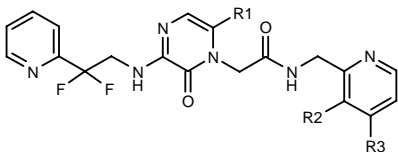
298610

2-[3-[2,2-Difluoro-2-(2-pyridinyl)ethylamino]-6-methyl-2-oxo-1,2-dihydropyrazin-1-yl]-N-(3-fluoropyridin-2-ylmethyl)acetamide



C20 H19 F3 N6 O2; Mol wt: 432.4041

ACTION – Anticoagulant, a thrombin inhibitor that is potentially useful for the treatment and prevention of thrombotic conditions, particularly coronary artery and cerebrovascular diseases. Other specifically claimed pyrazinone derivatives are:



Compound	R1	R2	R3	Formula
298614	Cl	F	H	C ₁₉ H ₁₆ ClF ₃ N ₆ O ₂
298615	Cl	SOMe	H	C ₂₀ H ₁₉ ClF ₂ N ₆ O ₃ S
298616	CN	F	H	C ₂₀ H ₁₆ F ₃ N ₇ O ₂
298617	Cl	F	Me	C ₂₀ H ₁₈ ClF ₃ N ₆ O ₂

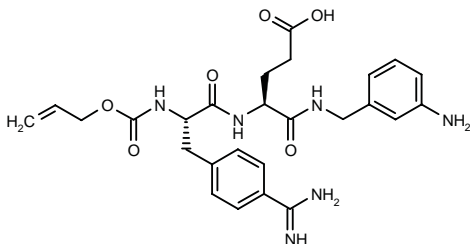
SOURCE – Merck & Co.

REFERENCES

1. Burgey, C.S. et al. (Merck & Co., Inc.) *Pyrazinone thrombin inhibitors*. WO 0075134.

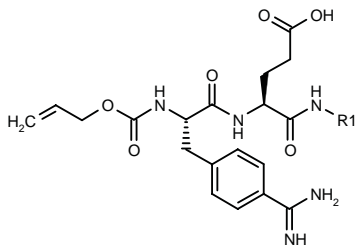
298623

N-(Allyloxycarbonyl)-4-amidino-L-phenylalanyl-L-glutamic acid N-(3-aminobenzyl)amide



C26 H32 N6 O6; Mol wt: 524.5748

ACTION – Factor VIIa inhibitor (K_i = 0.2 μ M in a chromogenic assay), with potential for the treatment and prophylaxis of thromboembolic diseases, cardiovascular disorders and restenosis. Other exemplified compounds include the following:



Compound	R1	Formula
298625	4-NH2-PhCH2	C ₂₆ H ₃₂ N ₆ O ₆
298629	3-Br-PhSO2NH(CH2)3	C ₂₈ H ₃₆ BrN ₆ O ₆ S
298633	4-MeO-PhSO2NH(CH2)3	C ₂₉ H ₃₈ N ₆ O ₆ S
298637	1-(3-Br-PhSO2)-4-Pip	C ₃₀ H ₃₇ BrN ₆ O ₆ S
298639	2-NH2-9H-9-fluorenyl	C ₃₂ H ₃₄ N ₆ O ₆

SOURCE – Aventis Pharma.

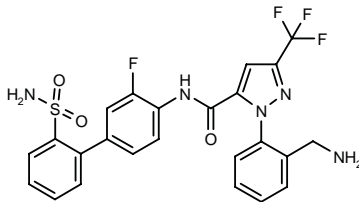
REFERENCES

1. Klinger, O. et al. (Aventis Pharma Deutschland GmbH) *Factor VIIa inhibitors*. EP 1059302, WO 0075172.

DPC-602

301563

1-[2-(Aminomethyl)phenyl]-N-(2'-sulfamoyl-3-fluorobiphenyl-4-yl)-3-(trifluoromethyl)-1 H-pyrazole-5-carboxamide



C24 H19 F4 N5 O3 S; Mol wt: 533.5041

ACTION – Potent, selective and orally available inhibitor of factor Xa with > 100-fold selectivity over other serine proteases. Compound was active in the arteriovenous shunt model of thrombosis in rabbit.

SOURCE – DuPont Pharmaceuticals.

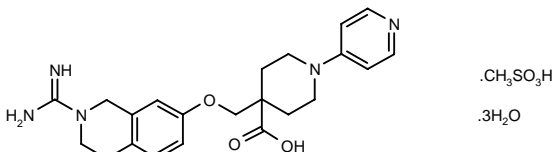
REFERENCES

- Galembo, R.A. Jr. et al. (DuPont Pharmaceuticals Co.) *Nitrogen containing heteroaromatics with ortho-substituted P1's as factor Xa inhibitors*. EP 1042229, WO 9932454.
- Galembo, R.A. Jr. et al. *Discovery of DPC602: Development of (4-methoxyphenyl)- and (2-(aminomethyl)phenyl)pyrazole inhibitors of factor Xa*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 15.
- Pruitt, J.R. et al. *Discovery of DPC602: Ortho-substituted phenylpyrazoles as potent, orally bioavailable inhibitors of factor X*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 49.

JTV-803*

283472

4-(2-Amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxymethyl)-1-(4-pyridinyl)piperidine-4-carboxylic acid methanesulfonate trihydrate



C22 H27 N5 O3 . C H4 O3 S . 3 H2 O; Mol wt: 559.6373

ACTION – Oral antithrombotic agent, a potent and selective inhibitor of human factor Xa with respective K_i values of 0.019, > 100, 13.6 and 78.2 μ M against factor Xa, thrombin, trypsin and plasmin. At i.v. doses of 0.1 mg/kg and above it significantly inhibited the thromboplastin-induced increase in plasma thrombin/antithrombin III complex in rats and its effect was comparable to that of argatroban (0.3 mg/kg/h) and low-molecular-weight heparin (LMWH; 100 U/kg/h). In rats, both compound and argatroban significantly inhibited thrombus formation in an arteriovenous shunt model (at 0.3-1 mg/kg/h) and prolonged the time to occlusion in a photoirradiation-induced arterial thrombosis model (at 1.5 mg/kg/h). JTV-803 induced significant prolongation of activated partial thromboplastin time (APTT) only at doses of 10 mg/kg/h and above and significant prolongation of

bleeding time at 30 mg/kg/h, while argatroban and LMWH exhibited significant effects at doses near the effective antithrombotic levels. In monkeys, compound significantly prolonged the time to occlusion in an arteriovenous shunt model following both i.v. (0.1 mg/kg/h) and oral (10 mg/kg) administration.

SOURCE – Japan Tobacco.

REFERENCES

1. Katoh, S. et al. (Japan Tobacco Inc.) *Amidine cpds.* EP 1070714, JP 2000136190, WO 9952895.

2. Asakura, H. et al. *Effect of JTV803, synthesized inhibitor of factor Xa and low molecular weight heparin against experimental disseminated intravascular coagulation in rats.* Int J Hematol 2000, 71(Suppl. 1): Abst 714.

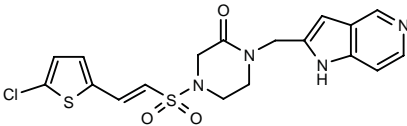
3. Hayashi, M. et al. *Antithrombotic effects of a synthetic inhibitor of activated factor X, JTV-803, in animals.* Eur J Pharmacol 2001, 412(1): 61.

*Identified compound **283472** (see **283471**) Drug Data Rep 2000, 022(01): 0038.

RPR-209685*

279378

4-[2-(5-Chlorothien-2-yl)vinylsulfonyl]-1-(1*H*-pyrrolo-[3,2-*c*]pyridin-2-ylmethyl)piperazin-2-one



C18 H17 Cl N4 O3 S2; Mol wt: 436.9423

ACTION – Anticoagulant and antithrombotic agent, a potent, selective and orally active inhibitor of factor Xa from a series of azaindoles.

SOURCE – Aventis Pharma.

REFERENCES

1. Ewing, W.R. et al. (Aventis Pharmaceuticals, Inc.) *Substd. oxoazaheterocyclyl factor Xa inhibitors.* EP 1051176, WO 9937304.

2. Ewing, W.R. et al. (Aventis Pharmaceuticals, Inc.) *Substd. oxoazaheterocyclyl factor Xa inhibitors.* WO 0032590, WO 0107436.

3. Mikol, P.V. et al. *Crystal structures of human factor Xa completed with potent inhibitors.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 24.

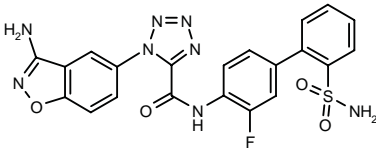
4. Poli, G.B. et al. *Design, SAR, and X-ray crystal structure of orally active azaindole inhibitors of factor Xa.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 68.

*Identified compound **279378** (see **279375**) Drug Data Rep 1999, 021(10): 0887.

SR-374

301820

1-(3-Amino-1,2-benzisoxazol-5-yl)-*N*-(3-fluoro-2'-sulfamoylbiphenyl-4-yl)-1*H*-tetrazole-5-carboxamide



C21 H15 F N8 O4 S; Mol wt: 494.4655

ACTION – Nonbenzamidine factor Xa inhibitor ($K_i = 0.35$ nM) potentially useful for the treatment of both arterial and venous thrombosis.

SOURCE – DuPont Pharmaceuticals.

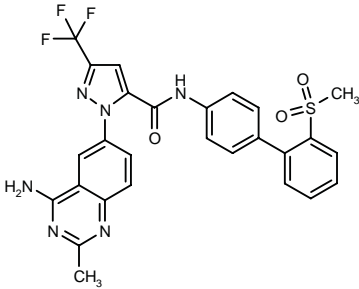
REFERENCES

1. Ellis, C.D. et al. *Nonbenzamidine tetrazole derivatives as factor Xa inhibitors.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 53.

SZ-042

301574

1-(4-Amino-2-methylquinazolin-6-yl)-*N*-[2'-(methylsulfonyl)biphenyl-4-yl]-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide



C27 H21 F3 N6 O3 S; Mol wt: 566.5619

ACTION – Potent and selective factor Xa inhibitor ($K_i = 1$ nM), an aminoquinazoline with > 1,600-fold selectivity over thrombin and trypsin and good oral bioavailability in dogs (F = 86%, $t_{1/2} = 1.8$ h).

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Li, R. et al. *Discovery of aminoquinazoline and aminoindazole P1 side chains as benzamidine mimics for FXa inhibitors.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 50.

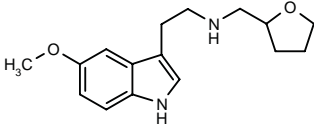
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

MLP-92

298520

N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]-*N*-(tetrahydrofuran-2-ylmethyl)amine



C16 H22 N2 O2; Mol wt: 274.3618

bleeding time at 30 mg/kg/h, while argatroban and LMWH exhibited significant effects at doses near the effective antithrombotic levels. In monkeys, compound significantly prolonged the time to occlusion in an arteriovenous shunt model following both i.v. (0.1 mg/kg/h) and oral (10 mg/kg) administration.

SOURCE – Japan Tobacco.

REFERENCES

1. Katoh, S. et al. (Japan Tobacco Inc.) *Amidine cpds.* EP 1070714, JP 2000136190, WO 9952895.

2. Asakura, H. et al. *Effect of JTV803, synthesized inhibitor of factor Xa and low molecular weight heparin against experimental disseminated intravascular coagulation in rats.* Int J Hematol 2000, 71(Suppl. 1): Abst 714.

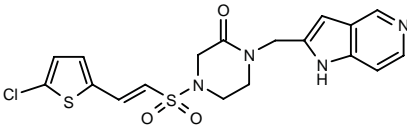
3. Hayashi, M. et al. *Antithrombotic effects of a synthetic inhibitor of activated factor X, JTV-803, in animals.* Eur J Pharmacol 2001, 412(1): 61.

*Identified compound **283472** (see **283471**) Drug Data Rep 2000, 022(01): 0038.

RPR-209685*

279378

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1. Ewing, W.R. et al. (Aventis Pharmaceuticals, Inc.) *Substd. oxoazaheterocyclyl factor Xa inhibitors.* EP 1051176, WO 9937304.

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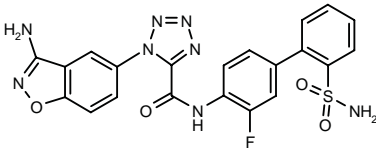
4. Poli, G.B. et al. *Design, SAR, and X-ray crystal structure of orally active azaindole inhibitors of factor Xa.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 68.

*Identified compound **279378** (see **279375**) Drug Data Rep 1999, 021(10): 0887.

SR-374

301820

1-(3-Amino-1,2-benzisoxazol-5-yl)-*N*-(3-fluoro-2'-sulfamoylbiphenyl-4-yl)-1*H*-tetrazole-5-carboxamide



C21 H15 F N8 O4 S; Mol wt: 494.4655

ACTION – Nonbenzamidine factor Xa inhibitor ($K_i = 0.35$ nM) potentially useful for the treatment of both arterial and venous thrombosis.

SOURCE – DuPont Pharmaceuticals.

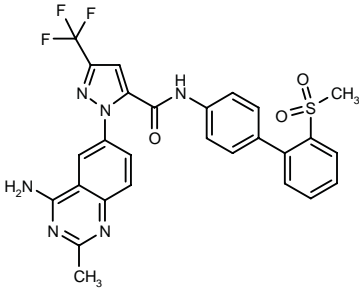
REFERENCES

1. Ellis, C.D. et al. *Nonbenzamidine tetrazole derivatives as factor Xa inhibitors.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 53.

SZ-042

301574

1-(4-Amino-2-methylquinazolin-6-yl)-*N*-[2'-(methylsulfonyl)biphenyl-4-yl]-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide



C27 H21 F3 N6 O3 S; Mol wt: 566.5619

ACTION – Potent and selective factor Xa inhibitor ($K_i = 1$ nM), an aminoquinazoline with > 1,600-fold selectivity over thrombin and trypsin and good oral bioavailability in dogs (F = 86%, $t_{1/2} = 1.8$ h).

SOURCE – DuPont Pharmaceuticals.

REFERENCES

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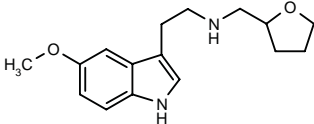
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

MLP-92

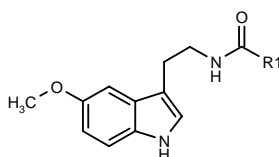
298520

N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]-*N*-(tetrahydrofuran-2-ylmethyl)amine



C16 H22 N2 O2; Mol wt: 274.3618

ACTION – A representative compound from a series of indole derivatives structurally related to melatonin that interact with the melatonergic system and selectively accumulate in the prostate, contrary to melatonin, which tends to accumulate in the pituitary, which makes them particularly useful for the treatment of prostatic conditions, especially benign and tumor prostate growth. *In vivo*, compound was shown to dose-dependently inhibit testosterone-induced prostate regrowth in adult castrated male rats following oral administration, being more potent than melatonin. Also reported to be useful for the treatment of impotence, cardiovascular, endocrine and CNS disorders, cancer, migraine and ophthalmological and dermatological diseases. Other exemplified compounds include the following:



Compound	R1	Formula
MLP-76 [298521]	2-furyl	C ₁₆ H ₁₆ N ₂ O ₃
MLP-77 [298522]	2-AcO-Ph	C ₂₀ H ₂₀ N ₂ O ₄
MLP-79 [298523]	2-THF	C ₁₆ H ₂₀ N ₂ O ₃

SOURCE – Neurim Pharmaceuticals.

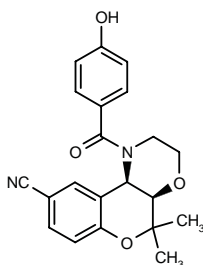
REFERENCES

1. Zisapel, N. and Laudon, M. (Neurim Pharmaceuticals Ltd.) *Indole derivs.* WO 0072815.

TREATMENT OF URINARY INCONTINENCE

300680

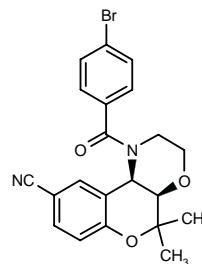
(-)-(4a*R*,10b*R*)-1-(4-Hydroxybenzoyl)-5,5-dimethyl-1,2,3,4a,5,10b-hexahydro[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitrile



C₂₁ H₂₀ N₂ O₄; Mol wt: 364.3990

ACTION – Bladder-selective potassium channel opener (IC₅₀ = 3.8 μM for relaxation of isolated rat detrusor strips exposed to extracellular KCl) with approximately 20-fold selectivity over K⁺ channels in the portal vein (IC₅₀ = 74.6 μM for relaxing spontaneous contractions). The relaxant activity on rat detrusor strips was antagonized by the potassium channel blocker gibenclamide, indicating a direct involvement of potassium channels. When compared with the reference compounds ZD-6169 and levocromakalim, compound showed slightly less relaxant activity on the detrusor but was at least 150-fold more

selective versus the blood vessel K⁺ channels. Potentially useful for the treatment of urinary incontinence. Another related compound is:



300679: C₂₁ H₁₉ Br N₂ O₃

SOURCE – National Taiwan University, Taipei (TW).

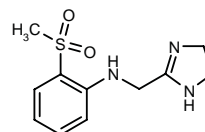
REFERENCES

1. Chiu, H.-I. et al. *N-Acyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano-[3,4-b][1,4]-oxazine-9-carbonitriles as bladder-selective potassium channel openers.* Bioorg Med Chem 2001, 9(2): 383.

GW-505524B

301691

N-(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)-*N*-[2-(methylsulfonyl)phenyl]amine



C₁₁ H₁₅ N₃ O₂ S; Mol wt: 253.3245

ACTION – Selective α_{1A}-adrenoceptor agonist potentially useful in the treatment of stress urinary incontinence.

SOURCE – GlaxoSmithKline.

REFERENCES

1. Bigham, E.C. et al. (Glaxo Group Ltd.) *Imidazoline derivs. as α_{1A} adrenoceptor ligands.* WO 0066563.

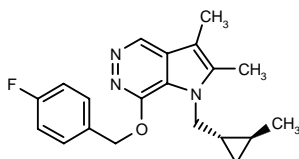
2. Bishop, M.J. et al. *Novel α_{1A}-selective anilinomethylimidazolines for the treatment of stress urinary incontinence.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 211.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

298918

7-(4-Fluorobenzyloxy)-2,3-dimethyl-1-[(1*S*,2*S*)-2-methyl-cyclopropylmethyl]-1*H*-pyrrolo[2,3-*d*]pyridazine



C₂₀ H₂₂ F N₃ O; Mol wt: 339.4118

ACTION – Antiulcer agent, an inhibitor of H⁺/K⁺-ATPase (IC₅₀ < 0.1 µg/ml against enzyme from pig stomach) with antimicrobial activity against *Helicobacter pylori* (MIC < 12.5 µg/ml against *H. pylori* strains 9470, 9472 and 9474). *In vivo*, compound was shown to inhibit gastric acid secretion stimulated by pylorus ligation in rats (ID₅₀ = 0.52 mg/kg p.o.). A representative compound from a series of optically active pyrrolopyridazine derivatives.

SOURCES – Sankyo; Ube.

REFERENCES

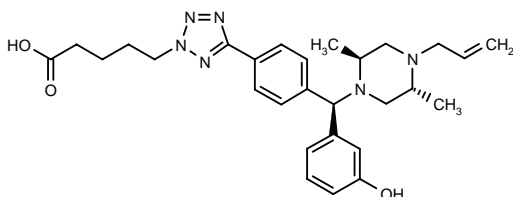
1. Hagihara, M. et al. (Ube Industries, Ltd.; Sankyo Co., Ltd.) *Optically active pyrrolopyridazine cpds.* JP 2001058993, WO 0077003.

AGENTS FOR IRRITABLE BOWEL SYNDROME THERAPY

UK-321130^{*,1,2}

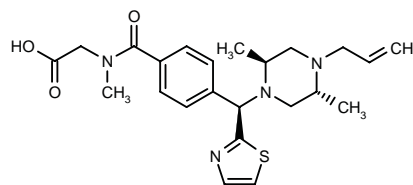
272176

(+)-5-[5-[4-[1(*R*)-[(2*S*,5*R*)-4-Allyl-2,5-dimethylpiperazin-1-yl]-1-(3-hydroxyphenyl)methyl]phenyl]-2*H*-tetrazol-2-yl]-pentanoic acid



C₂₈ H₃₆ N₆ O₃; Mol wt: 504.6314

ACTION – Nonpeptide delta opioid receptor agonist with high selectivity for peripheral over central receptors and good *in vivo* activity in preclinical models of gut motility, but devoid of centrally mediated side effects. Potentially useful for the treatment of irritable bowel syndrome. Another related compound is:



UK-328295 [301640]²: C₂₃ H₃₀ N₄ O₃ S

SOURCE – Pfizer.

REFERENCES

1. Maw, G.N. (Pfizer Ltd.; Pfizer Inc.) *Anti-inflammatory piperazinyl-benzyl-tetrazole derivs. and intermediates thereof.* EP 0983251, JP 2000513024, WO 9852929.

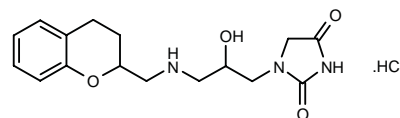
2. Maw, G.N. et al. *Discovery of non-peptide delta-opioid receptor agonists.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 168.

*Identified compound **272176** (see **272174**) Drug Data Rep 1999, 021(03): 0257.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

298618

1-[3-(3,4-Dihydro-2*H*-1-benzopyran-2-ylmethylamino)-2-hydroxypropyl]imidazolidine-2,4-dione hydrochloride



C₁₆ H₂₁ N₃ O₄ . HCl; Mol wt: 355.8198

ACTION – Fundic relaxant, as demonstrated in conscious dogs when given at 0.63 mg/kg s.c. or i.d., with little or no vasoconstrictor activity. Potentially useful for the treatment of conditions related to impaired relaxation of the fundus such as dyspepsia, early satiety, bloating and anorexia. A specifically claimed compound from a series of amino-alkyl-substituted benzodioxan, benzofuran and benzopyran derivatives.

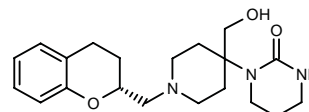
SOURCE – Janssen.

REFERENCES

1. Van Emelen, K. and De Bruyn, M.F.L. (Janssen Pharmaceutica NV) *Aminoalkyl substd. (benzodioxan, benzofuran or benzopyran) derivs.* WO 0075136.

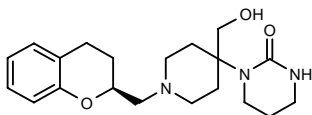
298620

1-[1-[3,4-Dihydro-2*H*-1-benzopyran-2(*R*)-ylmethyl]-4-(hydroxymethyl)piperidin-4-yl]hexahydropyrimidin-2-one

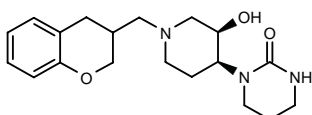


C₂₀ H₂₉ N₃ O₃; Mol wt: 359.4671

ACTION – Fundic relaxant, as demonstrated in conscious dogs when given at 0.63 mg/kg s.c. or i.d., with little or no vasoconstrictor activity. Potentially useful for the treatment of conditions related to impaired relaxation of the fundus such as dyspepsia, early satiety, bloating and anorexia. Other exemplified compounds from this series of pyrrolidinyl-, piperidinyl- or homopiperidinyl-substituted benzodioxan, benzofuran and benzopyran derivatives include the following:



298621: C₂₀ H₂₉ N₃ O₃



298622: C₁₉ H₂₇ N₃ O₃

SOURCE – Janssen.

REFERENCES

1. De Bruyn, M.F.L. et al. (Janssen Pharmaceutica NV) *Pyrrolidinyl, piperidinyl or homopiperidinyl substd. (benzodioxan, benzofuran or benzopyran) derivs.* WO 0075137.

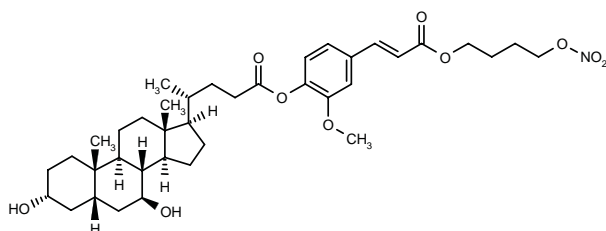
TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

NCX-1000

289301

(3 α ,5 β ,7 β)-3,7-Dihydroxycholan-24-oic acid 2-methoxy-4-[3-[4-(nitrooxy)butoxy]-3-oxo-1(*E*)-propenyl]phenyl ester

NO-UDCA



C₃₈ H₅₅ N O₁₀; Mol wt: 685.8495

ACTION – Nitric oxide (NO) derivative of ursodeoxycholic acid proven to protect against liver damage in a murine model of autoimmune hepatitis induced by i.v. injection of concanavalin A or the Fas agonist antibody Jo2, to inhibit IL-1 β , IL-18 and interferon gamma release and activation of caspases 3, 8 and 9. In HepG2 cells, compound induced reversible inhibition of proapoptotic caspases and was metabolized to release NO. Selected for clinical studies for the treatment of immune-mediated liver injury.

SOURCE – NicOx.

REFERENCES

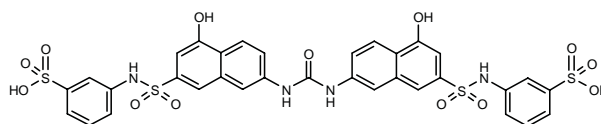
1. Del Soldato, P. (NicOx SA) *Pharmaceutical cpds.* WO 0061604.
2. Fiorucci, S. et al. *An NO derivative of ursodeoxycholic acid protects against Fas-mediated liver injury by inhibiting caspase activity.* Proc Natl Acad Sci USA 2001, 98(5): 2652.
3. Fiorucci, S. et al. *NCX-1000, a NO-derivative of ursodeoxycholic acid protects against Th1-mediated liver damage in mice.* Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A895.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

297889

3-[4-Hydroxy-7-[3-[5-hydroxy-7-(3-sulphophenylsulfamoyl)-naphthalen-2-yl]ureido]naphthalen-2-ylsulfonamido]-benzenesulfonic acid



C₃₃ H₂₆ N₄ O₁₃ S₄; Mol wt: 814.8474

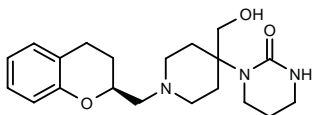
ACTION – Glucose uptake enhancer that acts by activating the autophosphorylation of the insulin receptor and is thus useful for the treatment of hyperglycemia and diabetes. It was found to stimulate insulin receptor phosphorylation in [³²P]-cytoplasmic kinase domain and whole-cell autophosphorylation assays, while it did not increase the phosphorylation of other receptors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and insulin-like growth factor type 1 (IGF-1) receptors. This compound was also shown to enhance insulin's ability to effect glucose transport into cultured fibroblasts (> 150% increase in glucose transport at 3.2 μ M) and lowered blood glucose levels in several animal models of diabetes. No acute toxicity was observed when this compound was administered i.p. to *db/db* mice and p.o. to CD rats at 300 mg/kg, which is about 10 times its effective dose.

SOURCE – Telik.

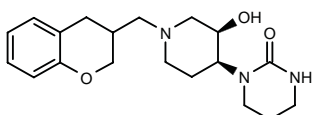
REFERENCES

1. Spevak, W. et al. (Telik, Inc.) *Novel naphthalene ureas as glucose uptake enhancers.* WO 0071506.

ACTION – Fundic relaxant, as demonstrated in conscious dogs when given at 0.63 mg/kg s.c. or i.d., with little or no vasoconstrictor activity. Potentially useful for the treatment of conditions related to impaired relaxation of the fundus such as dyspepsia, early satiety, bloating and anorexia. Other exemplified compounds from this series of pyrrolidinyl-, piperidinyl- or homopiperidinyl-substituted benzodioxan, benzofuran and benzopyran derivatives include the following:



298621: C₂₀ H₂₉ N₃ O₃



298622: C₁₉ H₂₇ N₃ O₃

SOURCE – Janssen.

REFERENCES

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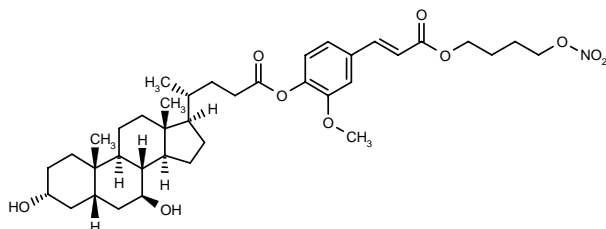
TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

NCX-1000

289301

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NO-UDCA



C₃₈ H₅₅ N O₁₀; Mol wt: 685.8495

ACTION – Nitric oxide (NO) derivative of ursodeoxycholic acid proven to protect against liver damage in a murine model of autoimmune hepatitis induced by i.v. injection of concanavalin A or the Fas agonist antibody Jo2, to inhibit IL-1 β , IL-18 and interferon gamma release and activation of caspases 3, 8 and 9. In HepG2 cells, compound induced reversible inhibition of proapoptotic caspases and was metabolized to release NO. Selected for clinical studies for the treatment of immune-mediated liver injury.

SOURCE – NicOx.

REFERENCES

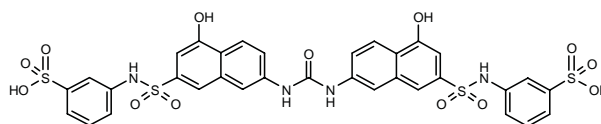
1. Del Soldato, P. (NicOx SA) *Pharmaceutical cpds.* WO 0061604.
2. Fiorucci, S. et al. *An NO derivative of ursodeoxycholic acid protects against Fas-mediated liver injury by inhibiting caspase activity.* Proc Natl Acad Sci USA 2001, 98(5): 2652.
3. Fiorucci, S. et al. *NCX-1000, a NO-derivative of ursodeoxycholic acid protects against Th1-mediated liver damage in mice.* Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A895.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

297889

3-[4-Hydroxy-7-[3-[5-hydroxy-7-(3-sulphophenylsulfamoyl)-naphthalen-2-yl]ureido]naphthalen-2-ylsulfonamido]-benzenesulfonic acid



C₃₃ H₂₆ N₄ O₁₃ S₄; Mol wt: 814.8474

ACTION – Glucose uptake enhancer that acts by activating the autophosphorylation of the insulin receptor and is thus useful for the treatment of hyperglycemia and diabetes. It was found to stimulate insulin receptor phosphorylation in [³²P]-cytoplasmic kinase domain and whole-cell autophosphorylation assays, while it did not increase the phosphorylation of other receptors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and insulin-like growth factor type 1 (IGF-1) receptors. This compound was also shown to enhance insulin's ability to effect glucose transport into cultured fibroblasts (> 150% increase in glucose transport at 3.2 μ M) and lowered blood glucose levels in several animal models of diabetes. No acute toxicity was observed when this compound was administered i.p. to *db/db* mice and p.o. to CD rats at 300 mg/kg, which is about 10 times its effective dose.

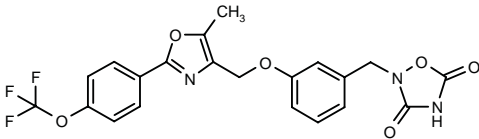
SOURCE – Telik.

REFERENCES

1. Spevak, W. et al. (Telik, Inc.) *Novel naphthalene ureas as glucose uptake enhancers.* WO 0071506.

300858

2-[3-[5-Methyl-2-[4-(trifluoromethoxy)phenyl]oxazol-4-ylmethoxy]benzyl]-1,2,4-oxadiazolidine-3,5-dione



C21 H16 F3 N3 O6; Mol wt: 463.3664

ACTION – Antihyperglycemic agent proven to significantly reduce plasma glucose and insulin levels in genetically obese *ob/ob* mice at an oral dose of 5 mg/kg (27 and 25% reduction, respectively, compared to control animals). In genetically diabetic *db/db* mice, compound at doses of 20 and 100 mg/kg induced a significant and dose-dependent reduction in plasma glucose.

SOURCES – Amgen; Wyeth-Ayerst.

REFERENCES

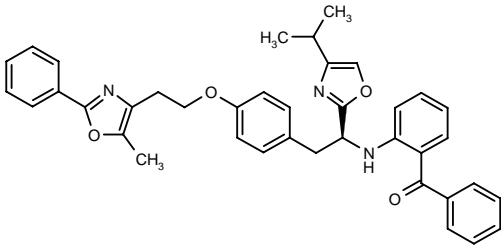
1. Malamas, M.S. et al. (American Home Products Corp.) *Aralkyl-1,2,4-oxadiazolidine-3,5-diones as antihyperglycemic agents*. US 5480896.

2. Malamas, M.S. et al. *Antihyperglycemic activity of new 1,2,4-oxadiazolidine-3,5-diones*. Eur J Med Chem 2001, 36(1): 31.

GW-3995

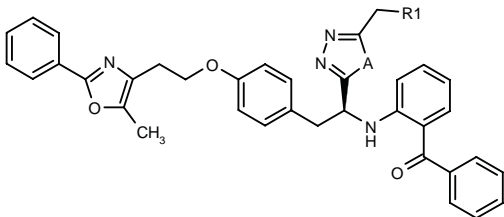
301577

1-[2-[1(*S*)-(4-Isopropylloxazol-2-yl)-2-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]ethylamino]phenyl]-1-phenylmethanone



C39 H37 N3 O4; Mol wt: 611.7383

ACTION – Antidiabetic agent, a derivative of the non-thiazolidinedione tyrosine-based antidiabetic agent GI-262570 (farglitazar) that acts as a peroxisome proliferator-activated receptor PPAR γ antagonist. Related PPAR γ antagonists include the following:



Compound	R1	A	Formula
GW-9765 [301579]	H	S	C ₃₆ H ₃₂ N ₄ O ₃ S
GW-5393 [301581]	Et	O	C ₃₈ H ₃₆ N ₄ O ₄

SOURCE – GlaxoSmithKline.

REFERENCES

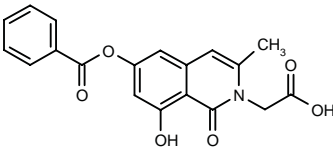
1. Cobb, J.E. et al. (Glaxo Group Ltd.) *Oxazole PPAR antagonists*. WO 0117994.

2. Shearer, B.G. et al. *Structure-based design and synthesis of PPAR γ antagonists*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 18.

TREATMENT OF DIABETIC COMPLICATIONS

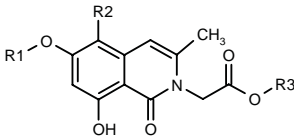
298275

2-[6-(Benzoyloxy)-8-hydroxy-3-methyl-1-oxo-1,2-dihydro-isoquinolin-2-yl]acetic acid



C19 H15 N O6; Mol wt: 353.3285

ACTION – Agent for the treatment of diabetic complications such as cataracts, retinopathy, neuropathy and nephropathy, an inhibitor of aldose reductase (IC₅₀ = 0.065 μ M against recombinant human muscular enzyme). Other compounds from this series of 1-oxoisoquinoline derivatives include the following:



Compound	R1	R2	R3	Formula
298276	Me	H	Me	C ₁₄ H ₁₅ NO ₅
298277	COPh	COPh	H	C ₂₈ H ₁₉ NO ₇
298278	H	H	H	C ₁₂ H ₁₁ NO ₅
298279	H	COPh	H	C ₁₉ H ₁₅ NO ₆

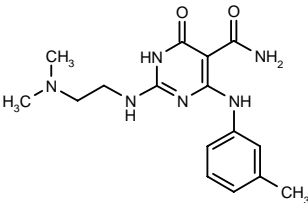
SOURCES – Mercian; Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

1. Nakajima, T. et al. (Microbial Chemistry Research Foundation;Mercian Corp.) *1-Oxoisoquinoline cpds. and their preparation method*. JP 2000309574.

298919

2-[2-(Dimethylamino)ethylamino]-6-(3-methylphenyl-amino)-4-oxo-3,4-dihydropyrimidine-5-carboxamide



C16 H22 N6 O2; Mol wt: 330.3898

ACTION – An inhibitor of protein kinase C (PKC), with potential for the treatment of diabetic complications such as diabetic nephropathy, neuropathy or retinopathy and cardiovascular diseases, as well as ischemic disorders, inflammation and cancer. *In vitro*, compound inhibited PKC in a scintillation proximity assay (SPA; IC₅₀ = 0.0049 μmol). It exhibited an IC₅₀ value of 0.38 μmol for inhibition of human PKCβ2 in a luciferase reporter gene assay using COS7 cells transfected with an activated human PKCβ2 expression vector. *In vivo*, it was shown to reduce urinary albumin excretion and to improve sciatic nerve conduction velocity deficits in streptozotocin-diabetic rats at 10 mg/kg/day p.o. x 8 weeks.

SOURCE – Yamanouchi.

REFERENCES

1. Suzuki, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel nitrogen-containing heterocyclic derivs. or salts thereof*. WO 0076980.

TREATMENT OF GYNECOLOGICAL DISORDERS

BNO-1055

300681

Cimicifuga racemosa extract which contains unidentified phytoestrogens

Klimadynon®

ACTION – Selective estrogen receptor modulator (SERM), a natural plant extract derived from *Cimifuga racemosa* proven to inhibit pituitary luteinizing hormone (LH) secretion and exert estrogenic effects in bone and aorta but not uterus. Potentially useful as estrogen replacement therapy for the treatment of postmenopausal syndrome.

SOURCES – Bionorica; Georg-August-Universität Göttingen, Göttingen (DE).

REFERENCES

1. Seidlova-Wuttke, D. et al. *Effects of Cimicifuga racemosa on estrogen-dependent tissues*. Phytomedicine 2000, 7(Suppl. 2): Abst SL-9b.

2. Seidlová-Wuttke, D. et al. *Evidence for selective estrogen receptor modulator (SERM) effects of the Cimicifuga racemosa (CR) extract BNO 1055*. Exp Clin Endocrinol Diabetes 2001, 109(Suppl. 1): Abst v066.

3. Seidova-Wuttke, D. and Wuttke, W. *Selective estrogen receptor modulator activity of Cimicifuga racemosa extract: Clinical data*. Phytomedicine 2000, 7(Suppl. 2): Abst SL-9a.

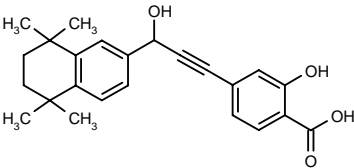
4. Wuttke, W. et al. *Selective estrogen receptor modulator (SERM) activity of the Cimicifuga racemosa extract BNO 1055: Pharmacology and mechanisms of action*. Phytomedicine 2000, 7(Suppl. 2): Abst SL-10.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

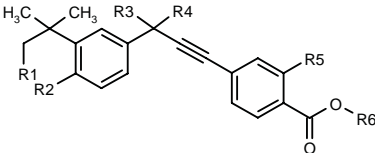
298131

2-Hydroxy-4-[3-hydroxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1-propynyl]benzoic acid

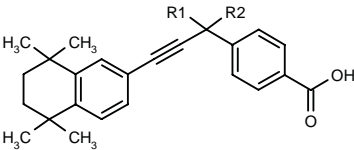


C24 H26 O4; Mol wt: 378.4654

ACTION – Agent with activity on cell differentiation and proliferation that is reported to be active in a test for differentiation of mouse embryonic teratocarcinoma cells and is therefore indicated for the treatment of dermatological keratinization disorders such as acne, ichthyoses, psoriasis, etc. Other exemplified polyaromatic propynyl compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
298132	-CH2C(Me)2-		OH	H	H	Me	C ₂₅ H ₂₈ O ₃
298133	-CH2C(Me)2-		OH	H	H	H	C ₂₄ H ₂₆ O ₃
298134	-CH2C(Me)2-		OH	H	OH	Me	C ₂₅ H ₂₈ O ₄
298135	H	OMe	-O-		OH	H	C ₂₁ H ₂₀ O ₅



Compound	R1	R2	Formula
298136		-O-	C ₂₄ H ₂₄ O ₃
298137	OH	H	C ₂₄ H ₂₆ O ₃

SOURCE – Galderma.

REFERENCES

1. Bernardon, J.-M. (CIRD Galderma) *Polyaromatic propynyl cpds. and pharmaceutical/cosmetic compsns. comprised thereof*. FR 2713635, US 6162445.

ACTION – An inhibitor of protein kinase C (PKC), with potential for the treatment of diabetic complications such as diabetic nephropathy, neuropathy or retinopathy and cardiovascular diseases, as well as ischemic disorders, inflammation and cancer. *In vitro*, compound inhibited PKC in a scintillation proximity assay (SPA; IC₅₀ = 0.0049 μmol). It exhibited an IC₅₀ value of 0.38 μmol for inhibition of human PKCβ2 in a luciferase reporter gene assay using COS7 cells transfected with an activated human PKCβ2 expression vector. *In vivo*, it was shown to reduce urinary albumin excretion and to improve sciatic nerve conduction velocity deficits in streptozotocin-diabetic rats at 10 mg/kg/day p.o. x 8 weeks.

SOURCE – Yamanouchi.

REFERENCES

1. Suzuki, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel nitrogen-containing heterocyclic derivs. or salts thereof*. WO 0076980.

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BNO-1055

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Klimadynon®

ACTION – Selective estrogen receptor modulator (SERM), a natural plant extract derived from *Cimifuga racemosa* proven to inhibit pituitary luteinizing hormone (LH) secretion and exert estrogenic effects in bone and aorta but not uterus. Potentially useful as estrogen replacement therapy for the treatment of postmenopausal syndrome.

SOURCES – Bionorica; Georg-August-Universität Göttingen, Göttingen (DE).

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1. Seidlova-Wuttke, D. et al. *Effects of Cimicifuga racemosa on estrogen-dependent tissues*. Phytomedicine 2000, 7(Suppl. 2): Abst SL-9b.

2. Seidlová-Wuttke, D. et al. *Evidence for selective estrogen receptor modulator (SERM) effects of the Cimicifuga racemosa (CR) extract BNO 1055*. Exp Clin Endocrinol Diabetes 2001, 109(Suppl. 1): Abst v066.

3. Seidova-Wuttke, D. and Wuttke, W. *Selective estrogen receptor modulator activity of Cimicifuga racemosa extract: Clinical data*. Phytomedicine 2000, 7(Suppl. 2): Abst SL-9a.

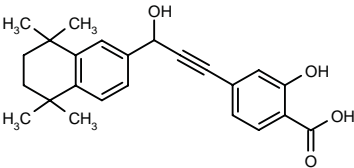
4. Wuttke, W. et al. *Selective estrogen receptor modulator (SERM) activity of the Cimicifuga racemosa extract BNO 1055: Pharmacology and mechanisms of action*. Phytomedicine 2000, 7(Suppl. 2): Abst SL-10.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

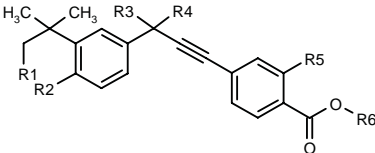
298131

2-Hydroxy-4-[3-hydroxy-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1-propynyl]benzoic acid

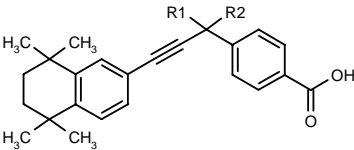


C24 H26 O4; Mol wt: 378.4654

ACTION – Agent with activity on cell differentiation and proliferation that is reported to be active in a test for differentiation of mouse embryonic teratocarcinoma cells and is therefore indicated for the treatment of dermatological keratinization disorders such as acne, ichthyoses, psoriasis, etc. Other exemplified polyaromatic propynyl compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
298132	-CH2C(Me)2-		OH	H	H	Me	C ₂₅ H ₂₈ O ₃
298133	-CH2C(Me)2-		OH	H	H	H	C ₂₄ H ₂₆ O ₃
298134	-CH2C(Me)2-		OH	H	OH	Me	C ₂₅ H ₂₈ O ₄
298135	H	OMe		-O-	OH	H	C ₂₁ H ₂₀ O ₅



Compound	R1	R2	Formula
298136		-O-	C ₂₄ H ₂₄ O ₃
298137	OH	H	C ₂₄ H ₂₆ O ₃

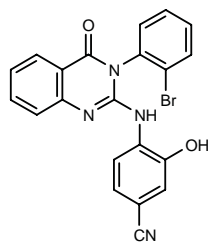
SOURCE – Galderma.

REFERENCES

1. Bernardon, J.-M. (CIRD Galderma) *Polyaromatic propynyl cpds. and pharmaceutical/cosmetic compsns. comprised thereof*. FR 2713635, US 6162445.

298368

4-[3-(2-Bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-ylamino]-3-hydroxybenzonitrile



C21 H13 Br N4 O2; Mol wt: 433.2637

ACTION – An inhibitor of the binding of chemokines such as IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, particularly IL-8, to the IL-8 receptor α (CXCR1) or β (CXCR2), with potential in the treatment of disorders characterized by excessive or unregulated IL-8 production including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, stroke, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft-vs.-host disease, Alzheimer’s disease, allograft rejection, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cell release. A specifically claimed compound from a series of cyclic guanidine derivatives.

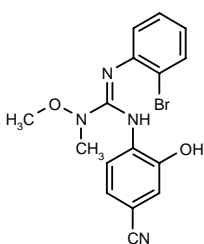
SOURCE – GlaxoSmithKline.

REFERENCES

1. Palovich, M.R. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0073282.

298369

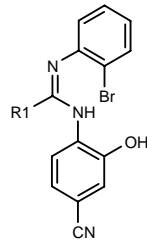
N''-(2-Bromophenyl)-N'-(4-cyano-2-hydroxyphenyl)-N-methyl-N-methoxyguanidine



C16 H15 Br N4 O2; Mol wt: 375.2245

ACTION – An inhibitor of the binding of chemokines such as IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, particularly IL-8, to the IL-8 receptor α (CXCR1) or β (CXCR2), with potential in the treatment of disorders characterized by excessive or unregulated IL-8 production including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, stroke, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft-vs.-host disease, Alzheimer’s disease, allograft rejection, malaria, restenosis, angiogenesis,

atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cell release. Other exemplified compounds from this series of tetraalkyl guanidine derivatives include the following:



Compound	R1	Formula
298370	N(i-Pr)2	C20H23BrN4O
298371	1-Pip	C19H19BrN4O
298372	1-pyrrolidinyl	C18H17BrN4O
298373	N(Et)2	C18H19BrN4O
298374	N(Me)Ph	C21H17BrN4O
298375	3-(CH2OH)-1-Pip	C20H21BrN4O2
298377	N(Me)CH2CH2N(Me)2	C19H22BrN5O
298378	N(Me)CH2NH2	C18H16BrN5O
298379	2-(1-Pip-CH2)-1-Pip	C26H30BrN5O
298380	2-[N(Me)2CH2]-1-Pip	C22H26BrN5O
298381	N(Me)(CH2)3N(Me)2	C20H24BrN5O

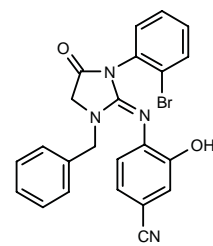
SOURCE – GlaxoSmithKline.

REFERENCES

1. Palovich, M.R. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0072800.

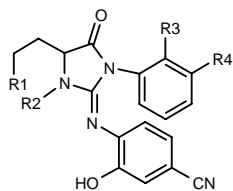
298382

4-[1-Benzyl-3-(2-bromophenyl)-4-oxoimidazolidin-2-ylideneamino]-3-hydroxybenzonitrile



C23 H17 Br N4 O2; Mol wt: 461.3173

ACTION – An inhibitor of the binding of chemokines such as IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, particularly IL-8, to the IL-8 receptor α (CXCR1) or β (CXCR2), with potential in the treatment of disorders characterized by excessive or unregulated IL-8 production including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, stroke, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft-vs.-host disease, Alzheimer’s disease, allograft rejection, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cell release. Other exemplified compounds from this series of cyclic guanidine derivatives include the following:



Compound	R1,R2	R3	R4	Isomer	Formula
298383	-SO2-	Br	H		C ₁₈ H ₁₃ BrN ₄ O ₄ S
298385	-CH2-	Br	H	R	C ₁₉ H ₁₆ BrN ₄ O ₂
298386	-CH2-	Cl	Cl	R	C ₁₉ H ₁₄ Cl ₂ N ₄ O ₂
298387	-CH2-	Br	H	S	C ₁₉ H ₁₆ BrN ₄ O ₂
298388	-(CH2)2-	Br	H		C ₂₀ H ₁₇ BrN ₄ O ₂

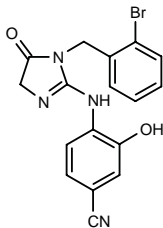
SOURCE – GlaxoSmithKline.

REFERENCES

1. Palovich, M.R. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0072845.

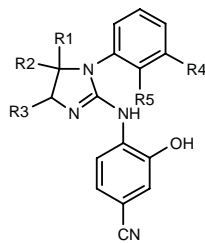
298389

4-[1-(2-Bromobenzyl)-5-oxo-4,5-dihydro-1*H*-imidazol-2-ylamino]-3-hydroxybenzonitrile

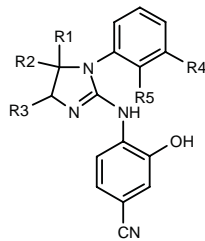


C17 H13 Br N4 O2; Mol wt: 385.2197

ACTION – An inhibitor of the binding of chemokines such as IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, particularly IL-8, to the IL-8 receptor α (CXCR1) or β (CXCR2), with potential in the treatment of disorders characterized by excessive or unregulated IL-8 production including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, stroke, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft-vs.-host disease, Alzheimer’s disease, allograft rejection, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cell release. Other exemplified compounds from this series of cyclic guanidine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
298391	H	H	H	H	Br	C ₁₆ H ₁₃ BrN ₄ O
298392	H		bond	H	Br	C ₁₆ H ₁₁ BrN ₄ O
298393		-O-	(R)-CH2CO2Et	H	Br	C ₂₀ H ₁₇ BrN ₄ O ₄
298394		-O-	(S)-i-Bu	Cl	Cl	C ₂₀ H ₁₈ Cl ₂ N ₄ O ₂
298395		-O-	(S)-CH2CH2CO2H	Cl	Cl	C ₁₉ H ₁₄ Cl ₂ N ₄ O ₄
298396	OMe	H	H	H	Br	C ₁₇ H ₁₅ BrN ₄ O ₂



298390: C15 H12 Br Cl N4 O3 S

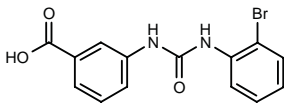
SOURCE – GlaxoSmithKline.

REFERENCES

1. Palovich, M.R. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0072840.

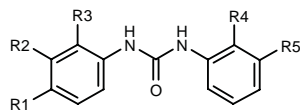
299049

3-[3-(2-Bromophenyl)ureido]benzoic acid



C14 H11 Br N2 O3; Mol wt: 335.1559

ACTION – Interleukin-8 (IL-8) receptor (CXCR1, CXCR2) antagonist claimed for the treatment of psoriasis, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis, undesired hematopoietic stem cell release and diseases caused by respiratory viruses, herpesviruses and hepatitis viruses. Other exemplified phenylureas include the following:



Compound	R1	R2	R3	R4	R5	Formula
299050	H	CH2CO2H	H	Br	H	C ₁₅ H ₁₃ BrN ₂ O ₃
299051	H	CH2CO2H	H	Cl	Cl	C ₁₅ H ₁₂ Cl ₂ N ₂ O ₃
299052	H	CO2H	H	Cl	Cl	C ₁₄ H ₁₀ Cl ₂ N ₂ O ₃
299053	H	CH2CH2CO2H	H	Cl	Cl	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₃
299054	Cl	CO2H	Cl	Br	H	C ₁₄ H ₉ BrCl ₂ N ₂ O ₃
299055	Cl	CO2H	H	Br	H	C ₁₄ H ₁₀ BrClN ₂ O ₃
299056	Cl	CO2H	H	Cl	Cl	C ₁₄ H ₉ Cl ₃ N ₂ O ₃
299057	Cl	CO2H	H	H	Cl	C ₁₄ H ₁₀ Cl ₂ N ₂ O ₃

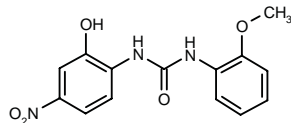
SOURCE – GlaxoSmithKline.

REFERENCES

1. Widdowson, K.L. and Benson, G.M. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0076515.

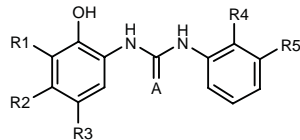
299065

N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyphenyl)urea



C14 H13 N3 O5; Mol wt: 303.2727

ACTION – Interleukin-8 (IL-8) receptor (CXCR1, CXCR2) antagonist claimed for the treatment of psoriasis, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis, undesired hematopoietic stem cell release and diseases caused by respiratory viruses, herpesviruses and hepatitis viruses. Other exemplified phenylureas include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
299066	H	NO2	H	SMe	H	O	C ₁₄ H ₁₃ N ₃ O ₄ S
299067	NO2	H	H	Br	H	O	C ₁₃ H ₁₀ BrN ₃ O ₄
299068	H	CN	H	OMe	H	O	C ₁₅ H ₁₃ N ₃ O ₃
299069	H	CN	H	CF3	H	O	C ₁₅ H ₁₀ F ₃ N ₃ O ₂
299070	H	NO2	H	Br	H	S	C ₁₃ H ₁₀ BrN ₃ O ₃ S
299071	Cl	Cl	H	Ph	H	O	C ₁₉ H ₁₄ Cl ₂ N ₂ O ₂
299072	H	H	NO2	Cl	Cl	O	C ₁₃ H ₉ Cl ₂ N ₃ O ₄

SOURCE – GlaxoSmithKline.

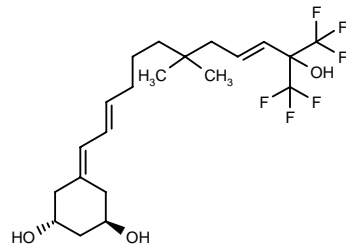
REFERENCES

1. Benson, G.M. et al. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0076495.

RO-65-2299*

280751

5-[12,12,12-Trifluoro-11-hydroxy-7,7-dimethyl-11-(tri-fluoromethyl)dodeca-2(E),9(E)-dienylidene]cyclohexane-1(R),3(R)-diol



C21 H30 F6 O3; Mol wt: 444.4530

ACTION – Oral antipsoriatic agent, a potent activator of the vitamin D receptor with an *in vitro* profile similar to that of calcitriol as regards inhibition of keratinocyte proliferation, immunomodulation and differentiation, but an improved therapeutic index (epidermal effect/calcemic effect) compared with calcitriol. The high oral availability and the moderate volume of distribution and plasma clearance make compound suitable for once-daily oral dosing. It did not exhibit signs of phototoxicity *in vitro* or *in vivo* and 13 weeks of repeated oral dosing was not associated with hypercalcemia up to 25 µg/kg/day in mice and rats and 200 µg/kg/day in dogs. Currently undergoing phase I studies in healthy volunteers.

SOURCE – Roche.

REFERENCES

1. Barbier, P. et al. (F. Hoffmann-La Roche AG) *Cyclohexanediol derivs*. EP 1056716, WO 9943646.

2. Bauer, F.W. et al. *Preclinical profile of the cyclohexanediol, RO 65-2299, a potential oral antipsoriatic*. 11th Workshop Vitamin D (May 27-June 1, Nashville) 2000, Abst 32.

3. Hilpert, H. and Wirz, B. *Novel versatile approach to an enantiopure 19-nor, des-C,D vitamin D-3 derivative*. Tetrahedron 2001, 57(4): 681.

4. Wirtz, B. et al. *Multiselective enzymatic reactions for the synthesis of protected homochiral cis- and trans-1,3,5-cyclohexanetriols*. Tetrahedron Asymmetry 2000, 11(20): 4171.

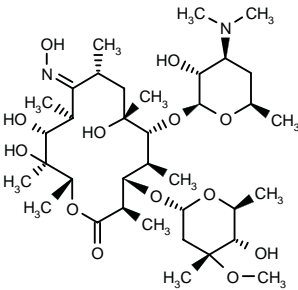
*Identified compound **280751** (see **280746**) Drug Data Rep 1999, 021(11): 0986.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

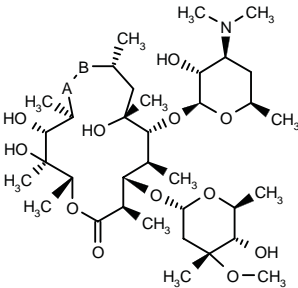
297951

(E)-13-Desethyl-13-methylerythromycin A 9-oxime

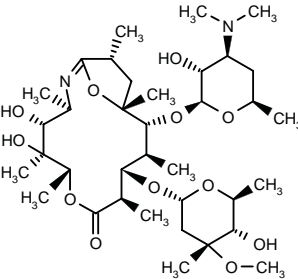


C36 H66 N2 O13; Mol wt: 734.9184

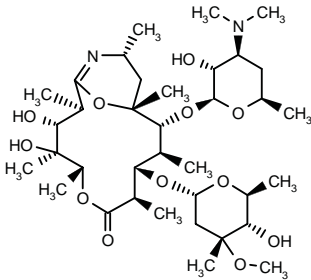
ACTION – Macrolide antibiotic that possesses activity against Gram-positive and Gram-negative bacteria, as well as protozoa. Other exemplified 13-methylerythromycins include the following:



Compound	A	B	Formula
297958	-NH-	-CH2-	C ₃₆ H ₆₈ N ₂ O ₁₂
297960	-N(Me)-	-CH2-	C ₃₇ H ₇₀ N ₂ O ₁₂
297961	-C(=NOH)-		C ₃₆ H ₆₆ N ₂ O ₁₃
297963	-CH2-	-NH-	C ₃₆ H ₆₈ N ₂ O ₁₂
297965	-CH2-	-N(Me)-	C ₃₇ H ₇₀ N ₂ O ₁₂



297955: C36 H64 N2 O12



297962: C36 H64 N2 O12

SOURCE – Pfizer.

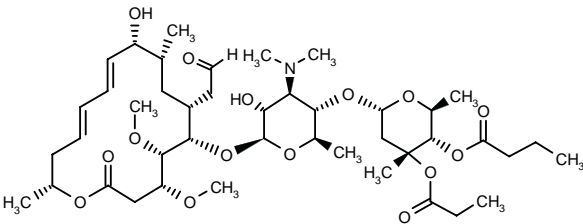
REFERENCES

1. Dirlam, J.P. et al. (Pfizer Products Inc.) 13-Methyl-erythromycin derivs. WO 0071557.

298450

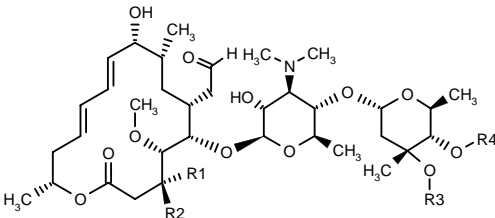
3-O-Methyl-3''-O-propionylleucomycin A5

[3*R*-(3α,4β,5α,6α,8α,10*E*,12*E*,15α)]-5-[3,6-Dideoxy-3-(dimethylamino)-4-*O*-(6-deoxy-4-*O*-butyryl-3-*C*-methyl-3-*O*-propionyl-α-L-mannopyranosyl)-β-D-glucopyranosyloxy]-9-hydroxy-6-(formylmethyl)-3,4-dimethoxy-8-methylhexadeca-10,12-dieno-15-lactone



C43 H71 N O15; Mol wt: 842.0259

ACTION – Antibacterial macrolide active against Gram-positive microorganisms, giving MIC values of 0.10, 0.20, 0.025, 0.05, 0.10, 0.025, 0.20 and 3.13 µg/ml, respectively, against *Staphylococcus aureus* 209P JC-1, *S. aureus* MS15027, *Micrococcus luteus* ATCC9341, *Streptococcus pneumoniae* DP1 type I, *S. pneumoniae* PRC-53, *Streptococcus pyogenes* Cook, *Moraxella catarrhalis* W-0500 and *Haemophilus influenzae* 9334. Other exemplified compounds from this series of 3-modified leucomycin derivatives include the following:



Compound	R1	R2	R3	R4	Formula
298451	allyl-O	H	COEt	COPr	C ₄₅ H ₇₃ NO ₁₅
298452	OMe	H	Me	i-BuCH2	C ₄₂ H ₇₃ NO ₁₃
298453	OMe	H	H	COEt	C ₃₉ H ₆₅ NO ₁₄
298454	OCOPh	H	H	COEt	C ₄₅ H ₆₇ NO ₁₅
298455	H	OCOPh	H	COEt	C ₄₅ H ₆₇ NO ₁₅

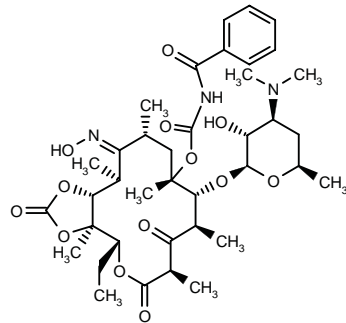
SOURCE – Meiji Seika.

REFERENCES

1. Kurihara, K. et al. (Meiji Seika Kaisha, Ltd.) 3-Modified leucomycin derivs. WO 0073317.

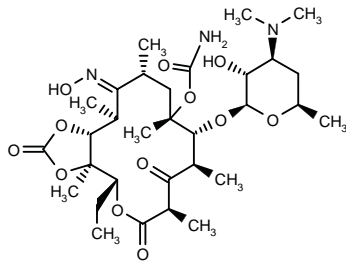
298732

6-O-(Benzamidocarbonyloxy)-3-des(hexopyranosyloxy)-3-oxoerythromycin A 11,12-cyclic carbonate 9-oxime



C38 H55 N3 O13; Mol wt: 761.8605

ACTION – Macrolide antibiotic with good antibacterial activity against a range of Gram-positive bacteria and some Gram-negative pathogens including *Staphylococcus aureus* A5177 (MIC = 0.39 µg/ml vs. 3.1 µg/ml for erythromycin A), *Staphylococcus epidermidis* 3519 (MIC = 0.39 µg/ml vs. 0.39 µg/ml for erythromycin A), *Streptococcus bovis* A5169 (MIC = 0.02 µg/ml vs. 0.02 µg/ml for erythromycin A), *Streptococcus agalactiae* CMX 508 (MIC = 0.02 µg/ml vs. 0.05 µg/ml for erythromycin A), *Streptococcus pyogenes* EES61 (MIC = 0.02 µg/ml vs. 0.05 µg/ml for erythromycin A), *Micrococcus luteus* ATCC4698 (MIC = 0.39 µg/ml vs. 0.2 µg/ml for erythromycin A), *Escherichia coli* SS (MIC = 0.39 µg/ml vs. 0.78 µg/ml for erythromycin A) and *Streptococcus pneumoniae* ATCC6303 (MIC = 0.03 µg/ml vs. 0.06 µg/ml for erythromycin A). Another compound from this series of 6-O-carbamate ketolide derivatives is:



298733: C31 H51 N3 O12

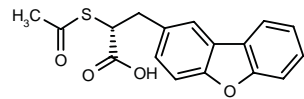
SOURCE – Abbott.

REFERENCES

1. Phan, L.T. et al. (Abbott Laboratories Inc.) 6-O-Carbamate ketolide derivs. WO 0075156.

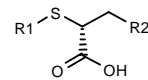
298877

2(R)-(Acetylsulfanyl)-2-(dibenzofuran-2-yl)propionic acid



C17 H14 O4 S; Mol wt: 314.3596

ACTION – Metallo-β-lactamase (MBL) inhibitor, potentially useful for the treatment of bacterial infections, preferably administered in combination with a β-lactam antibiotic, to overcome MBL-mediated resistance. This compound produced a 4-fold increase in sensitivity to a known carbapenem at 0.1 µM or less in an *Escherichia coli* strain that produces the metallo-β-lactamase IMP-1. Other exemplified thiol derivatives are:



Compound	R1	R2	Formula
298878	PhCO-D-Ala-	Ph	C ₁₉ H ₁₉ NO ₄ S
298879	PhCO-D-Ala-	4-Ph-Ph	C ₂₅ H ₂₃ NO ₄ S
298880	PhCO-D-Ala-	2-dibenzofuryl	C ₂₅ H ₂₁ NO ₅ S
298881	Ac-D-Ala-	4-Ph-Ph	C ₂₀ H ₂₁ NO ₄ S
298883	Ac-D-Ala-	2-dibenzofuryl	C ₂₀ H ₁₉ NO ₅ S
298884	PhCO	Ph	C ₁₆ H ₁₄ O ₃ S
298885	PhCO	4-Ph-Ph	C ₂₂ H ₁₈ O ₃ S
298886	PhCO	2-dibenzofuryl	C ₂₂ H ₁₆ O ₄ S
298887	Ac	Ph	C ₁₁ H ₁₂ O ₃ S
298888	Ac	4-Ph-Ph	C ₁₇ H ₁₆ O ₃ S

SOURCE – Merck & Co.

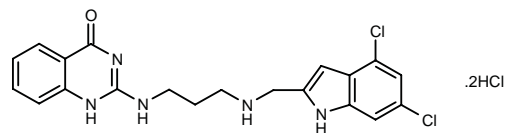
REFERENCES

1. Balkovec, J.M. et al. (Merck & Co., Inc.) Thiol deriv., metallo-β-lactamase inhibitors. WO 0076962.

ANTIBACTERIAL DRUGS

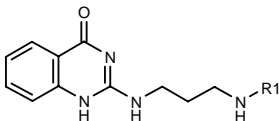
297980

2-[3-(4,6-Dichloro-1H-indol-2-ylmethylamino)propyl-amino]quinazolin-4(1H)-one dihydrochloride

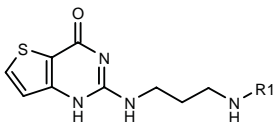


C20 H19 Cl2 N5 O . 2HCl; Mol wt: 489.2319

ACTION – Antibacterial agent that acts by inhibiting methionyl-tRNA synthetase (MRS, methionine–tRNA ligase; IC₅₀ in the range < 3-800 nM against *Staphylococcus aureus* MRS) and is selective with respect to the mammalian enzyme. It was active against strains of *S. aureus*, *Streptococcus pneumoniae* and *Enterococcus faecalis* (MIC < 1 mg/ml), and *Haemophilus influenzae*. Other specifically claimed compounds from this series of pyridones and pyrimidones include the following:



Compound	R1	Formula
297981	3-Br-5-MeO-7-indolyl-CH2	C ₂₁ H ₂₂ BrN ₅ O ₂
297983	3-Cl-5-MeO-7-indolyl-CH2	C ₂₁ H ₂₂ ClN ₅ O ₂
297988	6-Br-8-Cl-1,2,3,4-tetrahydro-4-quinolyl	C ₂₀ H ₂₁ BrClN ₅ O
297990	6,8-(Br)2-1,2,3,4-tetrahydro-4-quinolyl	C ₂₀ H ₂₁ Br ₂ N ₅ O
297992	3,5-(Br)2-2-[4-morpholinyl-(CH2)3O]-PhCH2	C ₂₅ H ₃₁ Br ₂ N ₅ O ₃
297994	2-EtO-3-Me-5-I-PhCH2	C ₂₁ H ₂₅ IN ₄ O ₂



Compound	R1	Formula
297982	3-Br-5-MeO-7-indolyl-CH2	C ₁₉ H ₂₀ BrN ₅ O ₂ S
297984	3-Cl-5-MeO-7-indolyl-CH2	C ₁₉ H ₂₀ ClN ₅ O ₂ S
297985	3-Cl-5-Me-7-indolyl-CH2	C ₁₉ H ₂₀ ClN ₅ OS
297986	6-Cl-8-I-3,4-dihydro-2H-1-benzopyran-4-yl	C ₁₈ H ₁₈ ClIN ₄ O ₂ S
297987	6,8-(Br)2-3,4-dihydro-2H-1-benzopyran-4-yl	C ₁₈ H ₁₈ Br ₂ N ₄ O ₂ S
297989	6,8-(Br)2-1,2,3,4-tetrahydro-4-quinolyl	C ₁₈ H ₁₈ Br ₂ N ₅ OS
297991	4,6-(Cl)2-2-indolyl-CH2	C ₁₈ H ₁₇ Cl ₂ N ₅ OS
297993	4,6-(Cl)2-1-(CH2CH2OH)-2-indolyl-CH2	C ₂₀ H ₂₁ Cl ₂ N ₅ O ₂ S

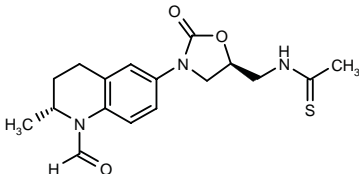
SOURCE – GlaxoSmithKline.

REFERENCES

1. Armstrong, S.A. et al. (SmithKline Beecham plc) *2-NH-Pyridones and pyrimidones as MRS inhibitors*. WO 0071524.

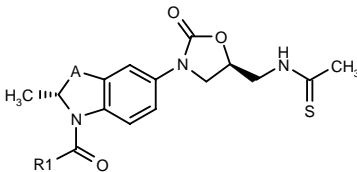
298210

N-[3-[1-Formyl-2(*R*)-methyl-1,2,3,4-tetrahydroquinolin-6-yl]-2-oxoxazolidin-5(*S*)-ylmethyl]thioacetamide



C17 H21 N3 O3 S; Mol wt: 347.4369

ACTION – Antibacterial agent with potent activity against both Gram-positive and Gram-negative bacteria including *Haemophilus influenza* and *Moraxella catarrhalis*. *In vitro*, compound exhibited MIC values of < 0.5 and 1 µg/ml against methicillin-sensitive *Staphylococcus aureus* UC 9213 and *M. catarrhalis* UC 30610, respectively. Other specifically claimed compounds from this series of bicyclic oxazolidinones include the following:



Compound	R1	A	Formula
298211	H	-CH2-	C ₁₆ H ₁₉ N ₃ O ₃ S
298212	CH2OH	-CH2-	C ₁₇ H ₂₁ N ₃ O ₄ S
298213	H	-CH2O-	C ₁₆ H ₁₈ N ₃ O ₄ S

SOURCE – Pharmacia.

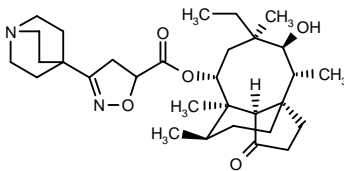
REFERENCES

1. Genin, M.J. et al. (Pharmacia Corp.) *Bicyclic oxazolidinones as antibacterial agent*. WO 0073301.

298234

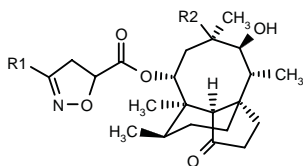
3-(1-Azabicyclo[2.2.2]oct-4-yl)-4,5-dihydroisoxazole-5-carboxylic acid (1*S*,2*R*,3*S*,4*R*,6*R*,7*R*,8*R*,14*R*)-4-ethyl-3-hydroxy-2,4,7,14-tetramethyl-9-oxotricyclo[5.4.3.0^{1,8}]-tetradec-6-yl ester

3-(1-Azabicyclo[2.2.2]oct-4-yl)-4,5-dihydroisoxazole-5-carboxylic acid (3*aS*,4*R*,5*S*,6*R*,8*R*,9*R*,9*aR*,10*R*)-6-ethyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3*a*,9-propano-3*aH*-cyclopentacycloocten-8-yl ester



C31 H48 N2 O5; Mol wt: 528.7292

ACTION – Antimicrobial agent reported to be useful for the treatment of infections caused by Gram-positive and Gram-negative bacteria and *Mycoplasma* including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Haemophilus* spp., *Neisseria* spp., *Legionella* spp., *Chlamydia* spp., *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Mycoplasma gallisepticum*. *In vitro*, compound is reported to exhibit MIC values in the range 0.06-4 µg/ml against *S. aureus* Oxford and *S. pneumoniae* R6. Other specifically claimed compounds from this series of isoxazoline carboxylate derivatives of mutilin are:



Compound	R1	R2	Isomer	Formula
298235	4-quinuclidinyl	Et	5R	C ₃₁ H ₄₈ N ₂ O ₅
298236	4-quinuclidinyl	Et	5S	C ₃₁ H ₄₈ N ₂ O ₅
298237	4-quinuclidinyl	vinyl		C ₃₁ H ₄₆ N ₂ O ₅
298238	4-quinuclidinyl	vinyl	5S	C ₃₁ H ₄₆ N ₂ O ₅
298239	4-quinuclidinyl	vinyl	5R	C ₃₁ H ₄₆ N ₂ O ₅
298241	1-Me-4-Pip	vinyl		C ₃₀ H ₄₆ N ₂ O ₅
298242	exo-8-Me-8-aza-bicyclo[3.2.1]oct-3-yl	vinyl		C ₃₂ H ₄₈ N ₂ O ₅

SOURCE – GlaxoSmithKline.

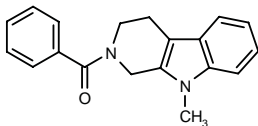
REFERENCES

1. Dean, D.K. et al. (SmithKline Beecham plc) *Isoxazoline carboxylate derivs. of mutiline and their use as antibacterials*. WO 0073287.

298334

2-Benzoyl-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indole

1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-2-yl)-1-phenylmethanone



C19 H18 N2 O; Mol wt: 290.3642

ACTION – Antibacterial agent representative of a series of tricyclic compounds that inhibit Fab I (previously known as EnvM).

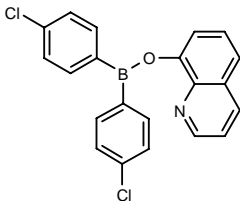
SOURCE – GlaxoSmithKline.

REFERENCES

1. Miller, W.H. et al. (SmithKline Beecham Corp.) *Antibacterial cpds*. WO 0072846.

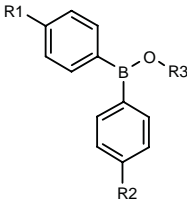
298606

Bis(4-chlorophenyl)borinic acid 8-quinolinylnyl ester



C21 H14 B Cl2 N O; Mol wt: 378.0646

ACTION – Broad-spectrum antibacterial agent that acts by specifically inhibiting bacterial adenine DNA methyl-transferases and exhibits little or no inhibitory effect on cytosine methyltransferases and hence has limited effects on eukaryotic, particularly mammalian, cells. *In vitro*, compound exhibited IC₅₀ values of 16 and 7 μM, respectively, against *Caulobacter crescentus* and *Bacillus subtilis*. Other specifically claimed compounds include the following:



Compound	R1=R2	R3	Formula
298607	F	8-quinolyl	C ₂₁ H ₁₄ BF ₂ NO
298608	F	CH2CH2NH2	C ₁₄ H ₁₄ BF ₂ NO
298938	Cl	CH2CH2NH2	C ₁₄ H ₁₄ BCl ₂ NO

SOURCE – Penn State Research Foundation, University Park, PA (US).

REFERENCES

1. Benkovic, S.J. et al. (Penn State Research Foundation) *DNA methyltransferase inhibitors*. WO 0075142.

BLF-487-529

298411

H-L-Phe-L-Ser-L-Gln-L-Ser-L-Cys-L-Ala-L-Pro-Gly-L-Ala-L-Asp-L-Pro-L-Lys-L-Ser-L-Arg-L-Leu-L-Cys-L-Ala-L-Leu-L-Cys-L-Ala-Gly-L-Asp-L-Asp-L-Gln-Gly-L-Leu-L-Asp-L-Lys-L-Cys-L-Val-L-Pro-L-Asn-L-Ser-L-Lys-L-Glu-L-Lys-L-Tyr-L-Tyr-Gly-L-Tyr-L-Thr-Gly-L-Ala-OH

C192 H297 N53 O65 S4; Mol wt: 4516.0280

ACTION – Antibacterial peptide that exhibits bacteriostatic activity against *Escherichia coli* ATCC 31705 and bactericidal activity against *E. coli* RIMD 0509939 0157;H7 and RIMD 0509861 0157;H7, *Salmonella enteritidis* 1891, *Listeria monocytogenes* IID 577 and *Yersinia enterocolitica* YE 98013 *in vitro*.

SOURCE – Meiji Milk Products.

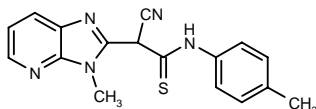
REFERENCES

1. Toba, T. et al. (Meiji Milk Products Co., Ltd.) *Anti-bacterial peptide*. JP 2000319300.

ANTIMYCOBACTERIAL AGENTS

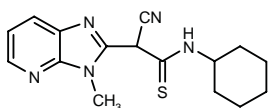
300387

2-Cyano-2-(3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)-*N*-(4-methylphenyl)thioacetamide



C17 H15 N5 S; Mol wt: 321.4065

ACTION – Antimycobacterial agent active *in vitro* against *Mycobacterium tuberculosis*, giving 73% inhibition at 12.5 µg/ml. Another related pyrido-imidazo-thiazine is:



300388: C16 H19 N5 S

SOURCE – Medical University of Gdansk, Gdansk (PL).

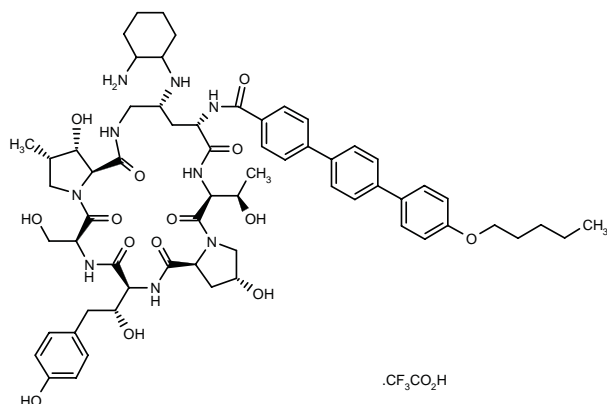
REFERENCES

1. Bukowski, L. *Some reactions of 2-cyanomethyl-3-methyl-3H-imidazo[4,5-b]pyridine with isothiocyanates. Antituberculous activity of the obtained compounds.* Pharmazie 2001, 56(1): 23.

ANTIFUNGAL AGENTS

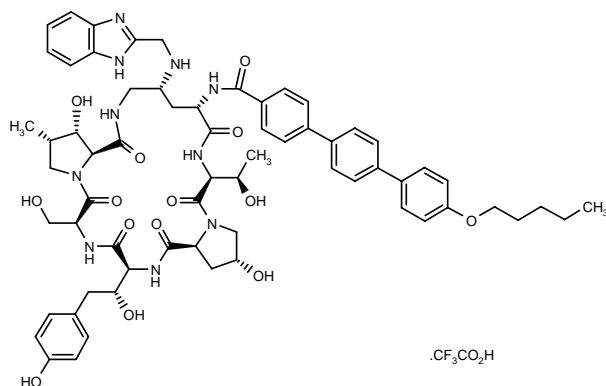
298677

N-[(2*R*,6*S*,9*S*,11*R*,14*aS*,15*S*,16*S*,20*S*,23*S*,25*aS*)-11-(2-Aminocyclohexylamino)-2,15-dihydroxy-6-[1(*R*)-hydroxyethyl]-23-[1(*R*)-hydroxy-2-(4-hydroxyphenyl)ethyl]-20-(hydroxymethyl)-16-methyl-5,8,14,19,22,25-hexaoxotetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'- η][1,4,7,10,13,16]-hexaazacyclohenicosin-9-yl]-4''-pentyloxy-1,1':4',1''-terphenyl-4-carboxamide trifluoroacetate isomer A



C63 H83 N9 O14 . C2 H F3 O2; Mol wt: 1304.4200

ACTION – Antifungal agent reported to potently inhibit *Candida albicans* glucan synthase *in vitro* and to be active against *C. albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida pseudotropicalis*, *Candida parapsilosis*, *Aspergillus fumigatus*, *Aspergillus flavus* and *Cryptococcus neoformans*. Another specifically claimed compound from this series of echinocandin derivatives is:



298678: C65 H78 N10 O14 . C2 H F3 O2

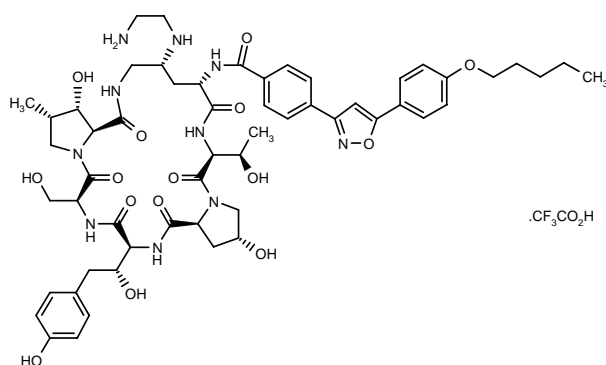
SOURCE – Aventis Pharma.

REFERENCES

1. Fauveau, P. et al. (Aventis Pharma SA) *Echinocandin derivs., method for preparing same and application as antifungal agents.* FR 2794746, WO 0075177.

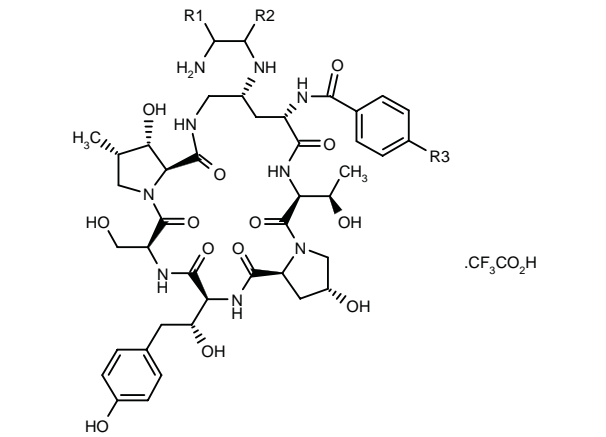
298680

N-[(2*R*,6*S*,9*S*,11*R*,14*aS*,15*S*,16*S*,20*S*,23*S*,25*aS*)-11-(2-Aminoethylamino)-2,15-dihydroxy-6-[1(*R*)-hydroxyethyl]-23-[1(*R*)-hydroxy-2-(4-hydroxyphenyl)ethyl]-20-(hydroxymethyl)-16-methyl-5,8,14,19,22,25-hexaoxotetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'- η][1,4,7,10,13,16]-hexaazacyclohenicosin-9-yl]-4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzamide trifluoroacetate



C56 H74 N10 O15 . C2 H F3 O2; Mol wt: 1241.2770

ACTION – Antifungal agent reported to potently inhibit *Candida albicans* glucan synthase *in vitro* and to be active against *C. albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida pseudotropicalis*, *Candida parapsilosis*, *Aspergillus fumigatus*, *Aspergillus flavus* and *Cryptococcus neoformans*. Other specifically claimed compounds from this series of echinocandin derivatives are:



Compound	R1	R2	R3	Formula
298681	-(CH2)4-		5-(4-C5H11O-Ph)-3-isoxazolyl	C ₆₂ H ₈₁ F ₃ N ₁₀ O ₁₇
298682	Me	H	5-(4-C5H11O-Ph)-3-isoxazolyl	C ₅₉ H ₇₇ F ₃ N ₁₀ O ₁₇
298683	H	H	5-(4-C5H11O-Ph)-1,3,4-thiadiazol-2-yl	C ₅₇ H ₇₄ F ₃ N ₁₁ O ₁₆ S
298684	-(CH2)4-		5-(4-C5H11O-Ph)-1,3,4-thiadiazol-2-yl	C ₆₁ H ₈₀ F ₃ N ₁₁ O ₁₆ S
298685	-(CH2)4-		3-(4-C5H11O-Ph)-1,2,4-oxadiazol-5-yl	C ₆₁ H ₈₀ F ₃ N ₁₁ O ₁₇

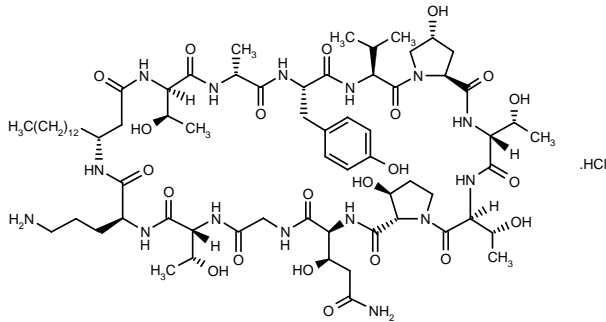
SOURCE – Aventis Pharma.

REFERENCES

1. Corbier, A. et al. (Aventis Pharma SA) *Novel echinocandin derivs., method for preparing same and use as antifungal agents*. FR 2794747, WO 0075178.

301154

Cyclo[D-alanyl-L-tyrosyl-L-valyl-4(R)-hydroxy-L-prolyl-D-allothreonyl-L-threonyl-3(S)-hydroxy-L-prolyl-3(R)-hydroxy-L-glutaminylglycyl-D-allothreonyl-L-ornithyl-3(S)-aminohexadecanoyl-D-allothreonyl] hydrochloride



C71 H117 N15 O22 . HCl; Mol wt: 1569.2490

ACTION – Antifungal agent, an analogue of the natural lipopeptide lactone antifungal FR-901469⁺ with comparable activity to FR-901469 and amphotericin B against *Aspergillus niger* (MIC = 0.5, 0.25 and 0.25 µg/ml, respectively).

SOURCE – Fujisawa.

REFERENCES

1. Tanaka, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel cpds*. JP 2000229998.

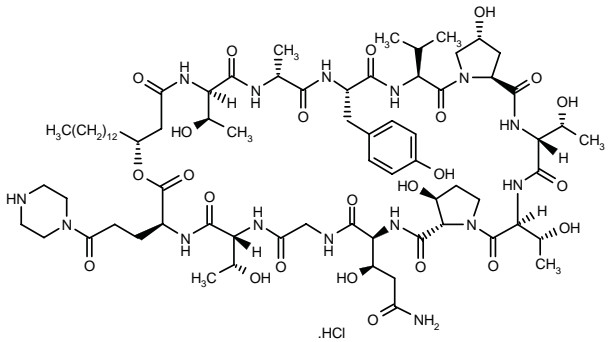
2. Barrett, D. et al. *An expedient synthesis of the amide analog of the potent antifungal lipopeptidolactone FR901469*. Tetrahedron Lett 2001, 42(4): 703.

*Drug Data Rep 1995, 017(04): 0363.

FR-203903

300327

[3S(1'R),6R(1'R),9S,11R,15S,18S,21R,24R(1'R),28R,31S,34R(1'R),40S(1'R),44S]-40-(2-Carbamoyl-1-hydroxyethyl)-11,44-dihydroxy-18-(4-hydroxybenzyl)-3,6,24,34-tetrakis(1-hydroxyethyl)-15-isopropyl-21-methyl-31-[3-oxo-3-(1-piperazinyl)propyl]-28-tridecyl-29-oxa-1,4,7,13,16,19,22,25,32,35,38,41-dodecaaza-tricyclo[41.3.0.0^{9,13}]hexatetracontane-2,5,8,14,17,20,23,26,30,33,36,39,42-tridecaone hydrochloride



C75 H121 N15 O24 . HCl; Mol wt: 1653.3230

ACTION – Antifungal agent, a cyclic depsipeptide active *in vitro* against *Candida* and *Aspergillus* spp. (MIC = 0.5-4 µg/ml) with potency comparable to amphotericin B. Compound showed excellent *in vivo* efficacy in a murine systemic *Candida albicans* infection with an ED₅₀ of 0.61 mg/kg (ED₅₀ amphotericin B = 0.13 mg/kg).

SOURCE – Fujisawa.

REFERENCES

1. Tanaka, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel cpds*. JP 2000229998.

2. Tanaka, A. et al. *Site-specific structural transformation of the novel antifungal cyclic depsipeptide FR901469: Synthesis and biological activity of FR203903*. J Antibiot 2001, 54(2): 193.

TKR-2462

298272

ACTION – Antifungal antibiotic isolated from *Penicillium* sp. TKR2462 (FERM P-17364), with MIC values of 3.12, 12.5 and > 100 µg/ml, respectively, against *Candida albicans* TIMM0136, *Candida kefir* TIMM0301 and *Cryptococcus neoformans* TIMM0354.

SOURCE – Takara Shuzo.

REFERENCES

1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Novel antibiotic TRK2462 and its preparation method*. JP 2000319292.

TKR-2993

298410

ACTION – Antifungal antibiotic isolated from *Cylindrocarpon* sp. TKR2993 (FERM P-17365), with MIC values of 12.5 and 100 µg/ml, respectively, against *Candida albicans* TIMM0136 and *Candida kefir* TIMM0301. No toxicity was observed following administration of 50 mg/kg i.p. to mice.

SOURCE – Takara Shuzo.

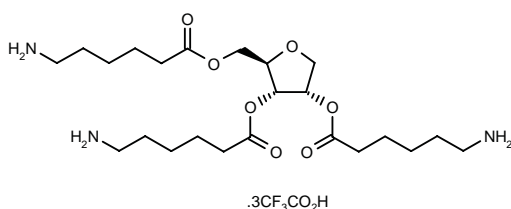
REFERENCES

1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Novel antibiotic TKR2993 and its preparation method*. JP 2000316592.

ANTIVIRAL DRUGS

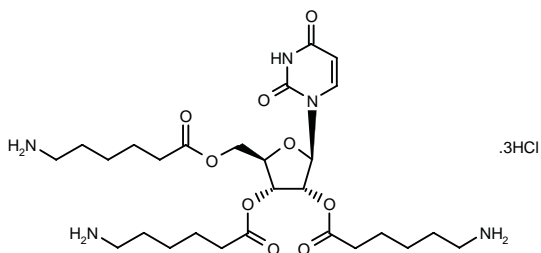
298092

2,3,5-Tris-*O*-(6-aminohexanoyl)-1-deoxy-D-ribose tris(trifluoroacetate)

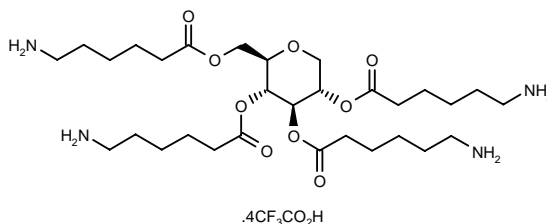


C₂₃ H₄₃ N₃ O₇ . 3 C₂ H F₃ O₂; Mol wt: 815.6724

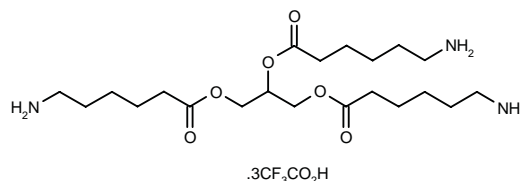
ACTION – Agent for the treatment or prevention of influenza infection that inhibits tryptase Clara, a protease found in Clara cells (IC₅₀ = 0.08 µg/ml). This protease is a trypsin-type serine protease found in the Clara cells of the bronchial epithelium and miniplasmin that specifically cleaves the precursor of fusion glycoprotein HA of influenza virus, resulting in activation of viral infectivity. Tryptase Clara inhibitors are thus suggested to be useful for the treatment or prevention of influenza infection. Other exemplified compounds are:



298093: C₂₇ H₄₅ N₅ O₉ . 3HCl



298094: C₃₀ H₅₆ N₄ O₉ . 4 C₂ H F₃ O₂



298095: C₂₁ H₄₁ N₃ O₆ . 3 C₂ H F₃ O₂

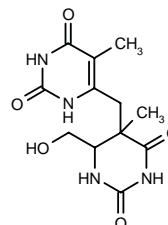
SOURCE – Sankyo.

REFERENCES

1. Kaneko, M. et al. (Sankyo Co., Ltd.) *Medicines containing basic cpds*. JP 2000302675.

298519

6-[4-(Hydroxymethyl)-5-methyl-2,6-dioxohexahydropyrimidin-5-ylmethyl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione



ACTION – Agent with antiviral activity, for example against herpes simplex virus type 1 (HSV-1) and varicella-zoster virus, as well as antitumor activity. A representative compound from a series of thymine derivatives.

SOURCE – Discovery Technologies.

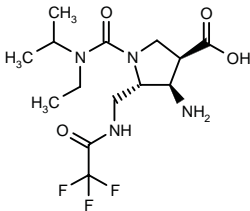
REFERENCES

1. Folkers, G. et al. (Discovery Technologies Ltd.) *Thymine derivs. that possess antiviral and antitumoral effects*. WO 0073281.

A-192558

301305

(±)-4(*R**)-Amino-1-(*N*-ethyl-*N*-isopropylcarbamoyl)-5(*S**)-(trifluoroacetamidomethyl)pyrrolidine-3(*R**)-carboxylic acid



C14 H23 F3 N4 O4; Mol wt: 368.3537

ACTION – Potent inhibitor of influenza neuraminidase (NA) with greater potency for influenza A NA over influenza B NA (IC₅₀ = 0.28 and 8 μM, respectively). Lead compound for further chemical manipulation in order to improve potency against both influenza A and B NA, as well as to optimize binding to the NA active site.

SOURCE – Abbott.

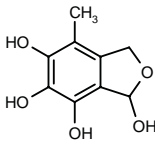
REFERENCES

1. Wang, G.T. et al. *Design, synthesis, and structural analysis of influenza neuraminidase inhibitors containing pyrrolidine cores*. J Med Chem 2001, 44(8): 1192.

FR-198248*

256459

4-Methyl-1,3-dihydro-2-benzofuran-1,5,6,7-tetraol



C9 H10 O5; Mol wt: 198.1730

ACTION – Antiinfluenza agent isolated from the culture broth of *Aspergillus terreus* No. 13830, proven to selectively inhibit influenza A and B virus replication in MDCK cells (IC₅₀ = 11 and 16.1 μM, respectively) while having no effect against herpes simplex virus type 1 (HSV-1) and vesicular stomatitis virus (IC₅₀ > 100 μM). In addition, compound exhibited strong *in vivo* efficacy, comparable to that of ribavirin, in a murine model of influenza A virus-induced respiratory tract infection (ED₅₀ = 1.98 and 2.30 mg/kg, respectively, intranasally once daily for 3 days). It appears to act by interfering with viral adsorption, although its precise mechanism has not yet been established.

SOURCE – Fujisawa.

REFERENCES

1. Nishihara, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *FR198248 and FR202306 substances*. JP 1997316090.

2. Nishihara, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *FR198248 substance*. JP 1997249679.

3. Nishihara, Y. et al. *FR198248, a new anti-influenza agent isolated from Aspergillus terreus No.13830. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activities*. J Antibiot 2001, 54(2): 136.

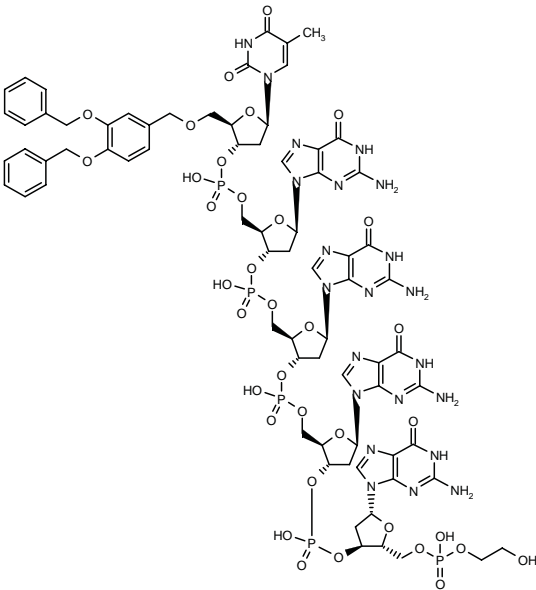
4. Nishihara, Y. et al. *New anti-influenza agents, FR198248 and its derivatives. II. Characterization of FR198248, its related compounds and some derivatives*. J Antibiot 2001, 54(3): 297.

*Identified compound **FR-198248** published without structure Drug Data Rep 1998, 020(02): 0154.

AIDS MEDICINES

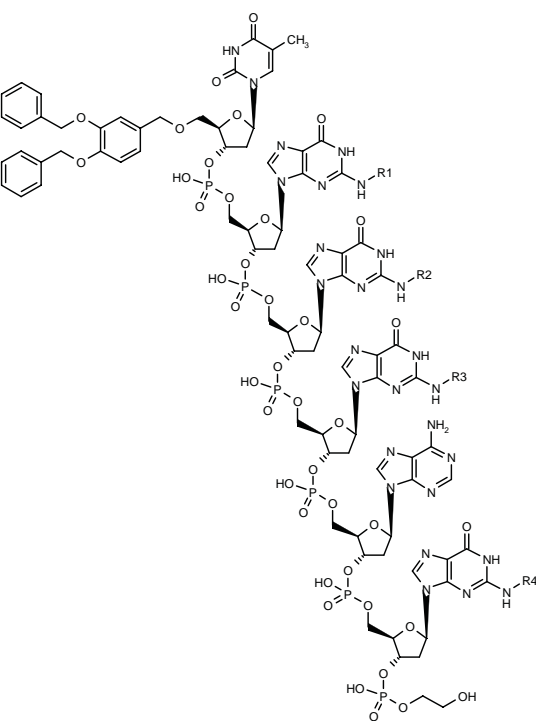
298073

5'-*O*-[3,4-Bis(benzyloxy)benzyl]thymidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→3')-2'-deoxy-5'-guanylic acid 5'-(2-hydroxyethyl) monoester

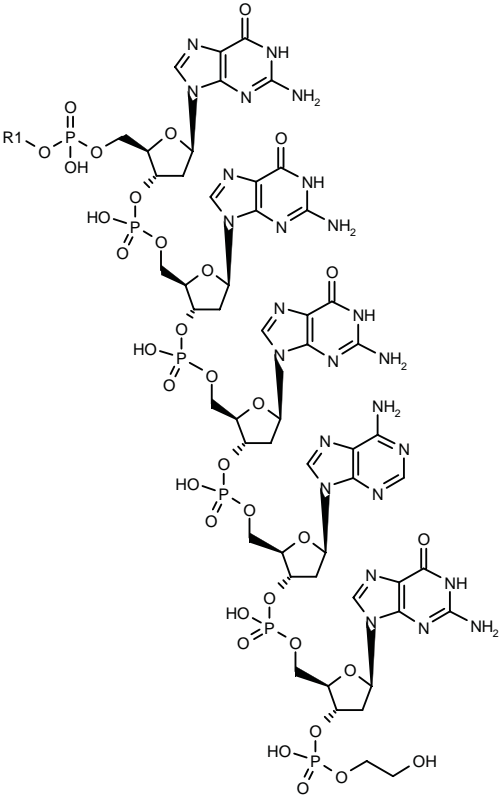


C73 H85 N22 O35 P5; Mol wt: 1985.4640

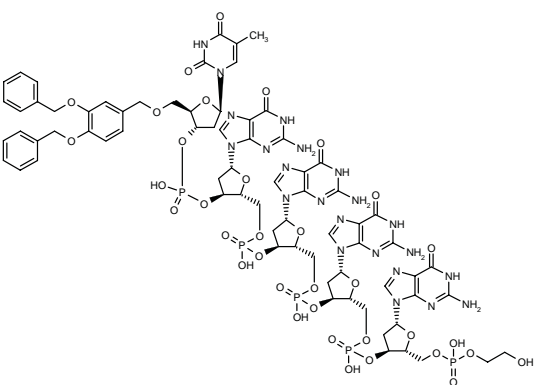
ACTION – Anti-HIV agent with an IC₅₀ value of 0.23 μg/ml for inhibition of HIV-1-induced cytopathic effect in MT-4 cells versus a CC₅₀ value for cytotoxicity in uninfected cells of > 50 μg/ml. Other exemplified oligo-deoxyribonucleotides are:



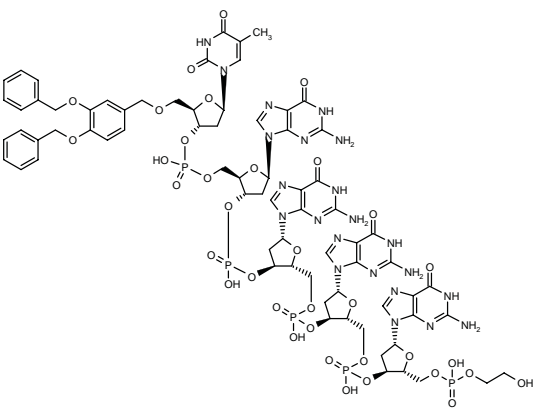
Compound	R1	R2	R3	R4	Formula
298084	Me	H	H	H	C ₈₄ H ₉₉ N ₂₇ O ₄₀ P ₆
298085	H	Me	H	H	C ₈₄ H ₉₉ N ₂₇ O ₄₀ P ₆
298086	H	H	Me	H	C ₈₄ H ₉₉ N ₂₇ O ₄₀ P ₆
298087	H	H	H	Me	C ₈₄ H ₉₉ N ₂₇ O ₄₀ P ₆
298088	Me	Me	Me	H	C ₈₆ H ₁₀₃ N ₂₇ O ₄₀ P ₆



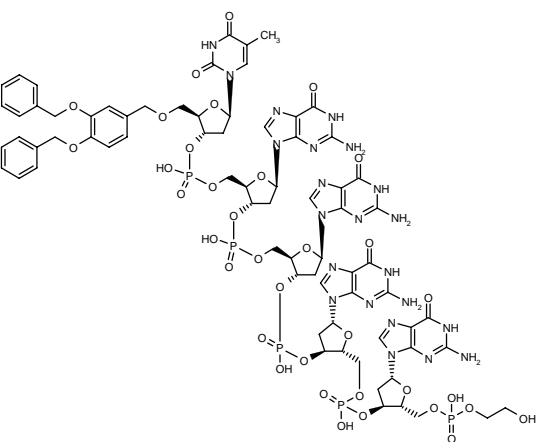
Compound	R1	Formula
298089	3,4-(PhCH ₂ O) ₂ -PhCH ₂ O(CH ₂) ₃	C ₇₆ H ₉₁ N ₂₅ O ₃₇ P ₆
298090	3,4-(PhCH ₂ O) ₂ -PhCH ₂ O(CH ₂) ₆	C ₇₉ H ₉₇ N ₂₅ O ₃₇ P ₆
298091	(2R,3S)-2-[3,4-(PhCH ₂ O) ₂ -PhCH ₂ OCH ₂]-3-furyl	C ₇₈ H ₉₃ N ₂₅ O ₃₈ P ₆



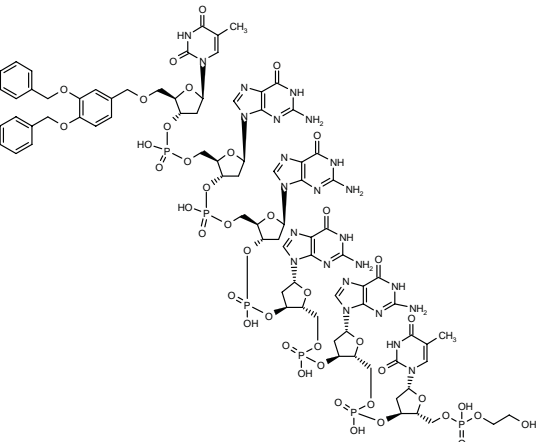
298076: C73 H85 N22 O35 P5



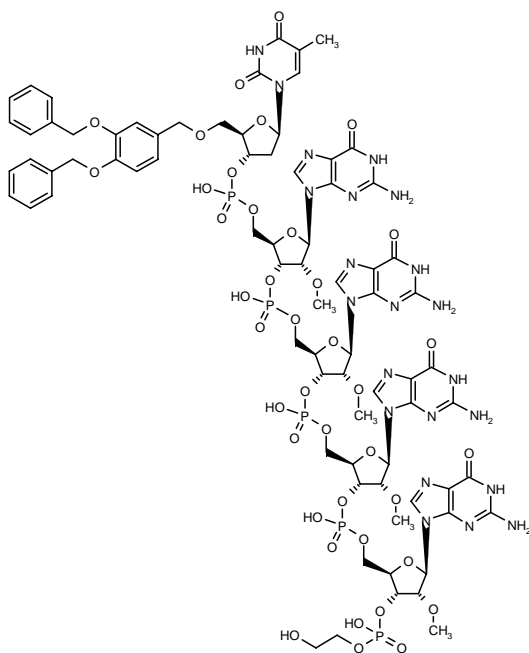
298077: C73 H85 N22 O35 P5



298078: C73 H85 N22 O35 P5



298080: C83 H98 N24 O42 P6



298083: C77 H93 N22 O39 P5

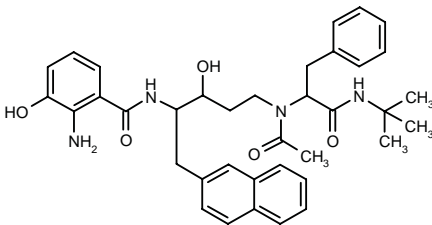
SOURCE – Sankyo.

REFERENCES

1. Koizumi, M. et al. (Sankyo Co., Ltd.) *Anti-AIDS agents containing oligodeoxy-ribonucleotide containing modified nucleoside and so on.* JP 2000302684.

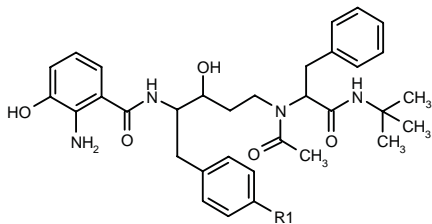
298079

N-[4-[*N*-Acetyl-*N*-[1-benzyl-2-(*tert*-butylamino)-2-oxo-ethyl]amino]-2-hydroxy-1-(2-naphthylmethyl)butyl]-2-amino-3-hydroxybenzamide



C37 H44 N4 O5; Mol wt: 624.7776

ACTION – Antiviral agent for AIDS with HIV protease-inhibitory activity (IC₅₀ = 29 nM against HIV protease from HTLV-IIIB virus expressed in *Escherichia coli*). Other compounds from this series of nonpeptide dipeptide analogues include the following:



Compound	R1	Formula
298081	H	C ₃₃ H ₄₂ N ₄ O ₅
298082	Ph	C ₃₉ H ₄₆ N ₄ O ₅

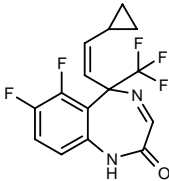
SOURCE – Sankyo.

REFERENCES

1. Nakamura, Y. et al. (Sankyo Co., Ltd.) *Non-peptidic dipeptide analogues.* JP 2000290242.

298517

5-[(*Z*)-2-Cyclopropylvinyl]-6,7-difluoro-5-(trifluoromethyl)-2,5-dihydro-1*H*-1,4-benzodiazepin-2-one



C15 H11 F5 N2 O; Mol wt: 330.2549

ACTION – Antiviral agent for AIDS with HIV reverse transcriptase-inhibitory activity, a representative compound from a series of 1,4-benzodiazepin-2-ones.

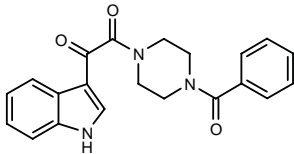
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Rodgers, J.D. et al. (DuPont Pharmaceuticals Co.) *1,4-Benzodiazepin-2-ones useful as HIV reverse transcriptase inhibitors.* WO 0073284.

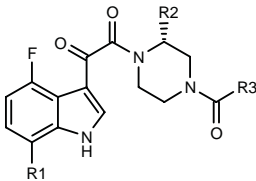
298856

2-(4-Benzoylpiperazin-1-yl)-1-(1*H*-indol-3-yl)ethane-1,2-dione



C21 H19 N3 O3; Mol wt: 361.3991

ACTION – Antiviral agent, particularly active against HIV, as demonstrated in HIV-1-infected MT-2 cells (> 98% inhibition at 10 μM). Other exemplified compounds from this series of indole-oxoacetyl piperazines include the following:



Compound	R1	R2	R3	Formula
298857	H	Me	Ph	C ₂₂ H ₂₀ FN ₃ O ₃
298858	H	H	3-thienyl	C ₁₉ H ₁₆ FN ₃ O ₃ S
298859	F	Me	2-Pyr	C ₂₁ H ₁₈ F ₂ N ₄ O ₃

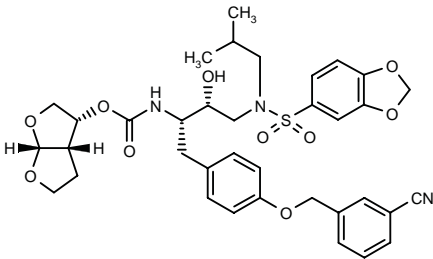
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Blair, W.S. et al. (Bristol-Myers Squibb Co.) *Antiviral indoleoxoacetyl piperazine derivs.* WO 0076521.

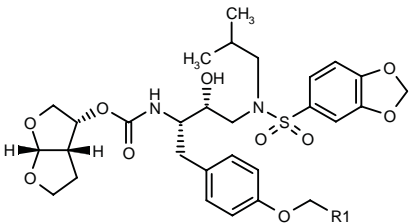
298860

N-[3-[*N*-(1,3-Benzodioxol-5-ylsulfonyl)-*N*-(isobutyl)amino]-1(*S*)-[4-(3-cyanobenzoyloxy)benzyl]-2(*R*)-hydroxypropyl]-carbamic acid (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester



C36 H41 N3 O10 S; Mol wt: 707.7969

ACTION – Anti-HIV agent, an HIV aspartyl protease inhibitor proven active against wild-type virus (IC₅₀ < 0.001 μM) and two multiprotease inhibitor-resistant viruses: the EP13 mutant (IC₅₀ < 0.001 μM) and D545701-14 mutant (IC₅₀ = 0.001-0.010 μM). Other exemplified sulfonamides include the following:



Compound	R1	Formula
298861	CH2NHCO2Me	C ₃₂ H ₄₃ N ₃ O ₁₂ S
298862	CH2CH2Ph	C ₃₇ H ₄₆ N ₂ O ₁₀ S
298863	CH2Ph	C ₃₆ H ₄₄ N ₂ O ₁₀ S
298864	2-Me-4-thiazolyl	C ₃₃ H ₄₁ N ₃ O ₁₀ S ₂

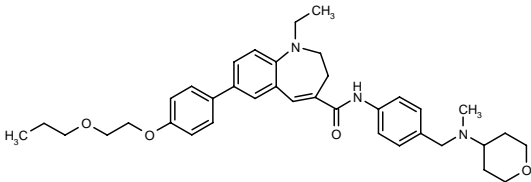
SOURCE – Vertex.

REFERENCES

1. Hale, M.R. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of aspartyl protease.* WO 0076961.

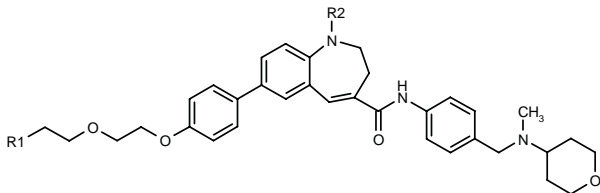
298933

1-Ethyl-*N*-[4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)-aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide



C37 H47 N3 O4; Mol wt: 597.7953

ACTION – Anti-HIV agent, a potent and selective chemokine CCR5 receptor antagonist (99% inhibition of [¹²⁵I]-RANTES binding in human CCR5-expressing CHO cells at 1 μM) proven to inhibit HIV-1 infection in MAGI-CCR5 cells. Other exemplified compounds from this series of benzazepine derivatives include the following:



Compound	R1	R2	Formula
298935	H	CHO	C ₃₅ H ₄₁ N ₃ O ₅
298936	Me	CHO	C ₃₆ H ₄₃ N ₃ O ₅
298937	H	Et	C ₃₆ H ₄₆ N ₃ O ₄

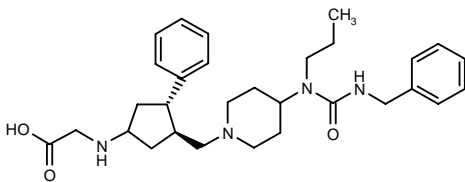
SOURCE – Takeda.

REFERENCES

1. Shiraishi, M. et al. (Takeda Chemical Industries, Ltd.) *Benzazepine derivs., process for the preparation of the same and uses thereof.* JP 2001058992, WO 0076993.

299011

N-[4(*S*)-[4-(3-Benzyl-1-propylureido)piperidin-1-ylmethyl]-3(*S*)-phenylcyclopentyl]glycine



C30 H42 N4 O3; Mol wt: 506.6868

ACTION – Modulator of chemokine receptors, particularly CCR3 and/or CCR5, expected to be useful for the treatment and prevention of HIV infection and AIDS, as well as in the treatment of inflammatory and immune disorders such as allergic rhinitis, dermatitis, conjunctivitis, asthma, rheumatoid arthritis and atherosclerosis.

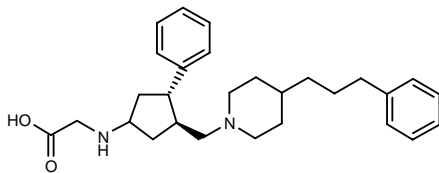
SOURCE – Merck & Co.

REFERENCES

1. Finke, P.E. et al. (Merck & Co., Inc.) *N-Cyclopentyl modulators of chemokine receptor activity.* WO 0076973.

299016

N-[3(*S*)-Phenyl-4(*S*)-[4-(3-phenylpropyl)piperidin-1-yl-methyl]cyclopentyl]glycine



C₂₈ H₃₈ N₂ O₂; Mol wt: 434.6202

ACTION – Modulator of chemokine receptors, particularly CCR3 and/or CCR5, expected to be useful for the treatment and prevention of HIV infection and AIDS, as well as in the treatment of inflammatory and immune disorders such as allergic rhinitis, dermatitis, conjunctivitis, asthma, rheumatoid arthritis and atherosclerosis.

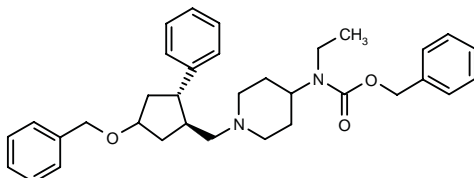
SOURCE – Merck & Co.

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299017

N-[1-[(1*S*,2*S*)-4-(Benzyloxy)-2-phenylcyclopentylmethyl]-piperidin-4-yl]-*N*-ethylcarbamic acid benzyl ester



C₃₄ H₄₂ N₂ O₃; Mol wt: 526.7168

ACTION – Modulator of chemokine receptors, particularly CCR3 and/or CCR5, expected to be useful for the treatment and prevention of HIV infection and AIDS, as well as in the treatment of inflammatory and immune disorders such as allergic rhinitis, dermatitis, conjunctivitis, asthma, rheumatoid arthritis and atherosclerosis.

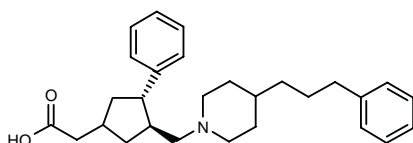
SOURCE – Merck & Co.

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299018

2-[3(*S*)-Phenyl-4(*S*)-[4-(3-phenylpropyl)piperidin-1-yl-methyl]cyclopentyl]acetic acid



C₂₈ H₃₇ N O₂; Mol wt: 419.6053

ACTION – Modulator of chemokine receptors, particularly CCR3 and/or CCR5, expected to be useful for the treatment and prevention of HIV infection and AIDS, as well as in the treatment of inflammatory and immune disorders such as allergic rhinitis, dermatitis, conjunctivitis, asthma, rheumatoid arthritis and atherosclerosis.

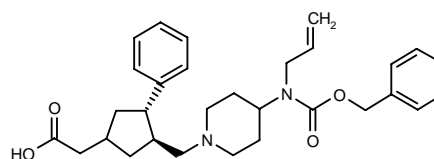
SOURCE – Merck & Co.

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299019

2-[4(*S*)-[4-[*N*-Allyl-*N*-(benzyloxycarbonyl)amino]piperidin-1-ylmethyl]-3(*S*)-phenylcyclopentyl]acetic acid



C₃₀ H₃₈ N₂ O₄; Mol wt: 490.6402

ACTION – Modulator of chemokine receptors, particularly CCR3 and/or CCR5, expected to be useful for the treatment and prevention of HIV infection and AIDS, as well as in the treatment of inflammatory and immune disorders such as allergic rhinitis, dermatitis, conjunctivitis, asthma, rheumatoid arthritis and atherosclerosis.

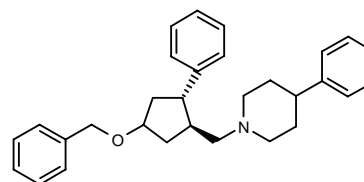
SOURCE – Merck & Co.

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299020

1-[(1*S*,2*S*)-4-(Benzyloxy)-2-phenylcyclopentylmethyl]-4-phenylpiperidine



C₃₀ H₃₅ N O; Mol wt: 425.6125

ACTION – Modulator of chemokine receptors, particularly CCR3 and/or CCR5, expected to be useful for the treatment and prevention of HIV infection and AIDS, as well as in the treatment of inflammatory and immune disorders such as allergic rhinitis, dermatitis, conjunctivitis, asthma, rheumatoid arthritis and atherosclerosis.

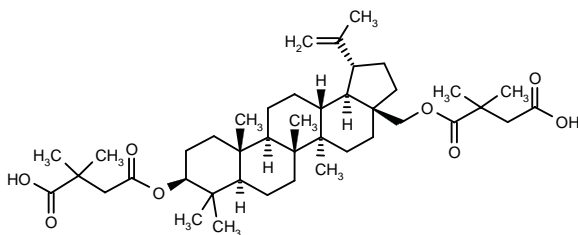
SOURCE – Merck & Co.

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299217

3-*O*-(3,3-Dimethylsuccinyl)-28-*O*-(2,2-dimethylsuccinyl)lup-20(29)-en-3 β ,28-diol



C42 H66 O8; Mol wt: 698.9754

ACTION – Anti-HIV agent, a betulinic acid derivative shown to strongly inhibit HIV-1 replication in acutely infected H9 cells with an EC₅₀ value of 0.87 nM compared to an EC₅₀ of 45 nM for zidovudine. Compound showed very low cytotoxicity in mock-infected H9 cells (IC₅₀ = 36.9 μ M), with a therapeutic index similar to that of zidovudine.

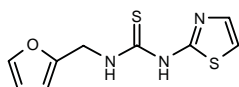
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2. Kashiwada, Y. et al. Study of a natural anti HIV substance. The anti HIV activity of an isomer of 3,28-di-*O*-(dimethylsuccinyl)-betulin. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abstr 29(PB)II-001.

300463

N-(2-Furylmethyl)-*N'*-(2-thiazolyl)thiourea



C9 H9 N3 O S2; Mol wt: 239.3221

ACTION – Antiviral agent for AIDS, a non-nucleoside reverse transcriptase inhibitor (NNRTI) with strong antiviral activity against both wild-type (IC₅₀ < 0.001 μ M in HIV-1-infected peripheral blood mononuclear cells) and two NNRTI-resistant HIV-1 isolates (IC₅₀ = 2.0 and 0.6 μ M against A7 and A17 variant, respectively). Compound was more active than nevirapine and delavirdine against wild-type (IC₅₀ = 0.034 and 0.009 μ M, respectively) and particularly the NNRTI-resistant HIV-1 strains (IC₅₀ > 50 μ M against A7 and A17 variant). Low cytotoxicity was seen against peripheral blood mononuclear cells (selectivity index > 100,000).

SOURCE – Parker Hughes Institute, Roseville, MN (US).

REFERENCES

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ATBI

300629

L-Alanyl-glycyl-L-lysyl-L-lysyl-L-aspartyl-L-aspartyl-L-aspartyl-L-aspartyl-L-prolyl-L-prolyl-L-glutamic acid

C48 H75 N13 O22; Mol wt: 1186.1890

ACTION – Noncompetitive and tight-binding inhibitor of HIV-1 protease (K_i = 17.8 nM) isolated from an extremophilic *Bacillus* sp., proven to bind to the active site of HIV-1 protease and to inactivate the enzyme by impairing the flexibility of the flaps, thereby limiting access of the substrate to the active site of the enzyme. Useful lead for a novel class of HIV-1 protease inhibitors.

SOURCE – National Chemical Laboratory, Pune (IN).

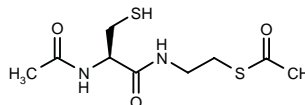
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I-152

298281

Thioacetic acid *S*-[2-(*N*-acetyl-L-cysteinylamino)ethyl] ester



C9 H16 N2 O3 S2; Mol wt: 264.3684

ACTION – Antioxidant that acts by increasing the intracellular and/or extracellular levels of glutathione (GSH), potentially useful for the treatment of disorders related to depleted GSH levels, particularly viral infections, respiratory, neurodegenerative, cardiovascular and autoimmune disorders, cancer, diabetes, and eye and skin disorders. Compound exhibited antiviral activity in HIV-infected monocyte-derived macrophages (MDM; IC₅₀ = 50 μ M), being more potent than the known compounds *N*-acetyl-L-cysteine (NAC; IC₅₀ = 9.4 mM) and cysteamine (MEA; IC₅₀ = 300 μ M). In addition, it was found to be about 120-fold more potent than NAC in increasing GSH levels. A representative compound from a series of *N*-acyl-L-cysteine derivatives.

SOURCES – CNRS; Commissariat à l'Energie Atomique, Orsay Cedex (FR).

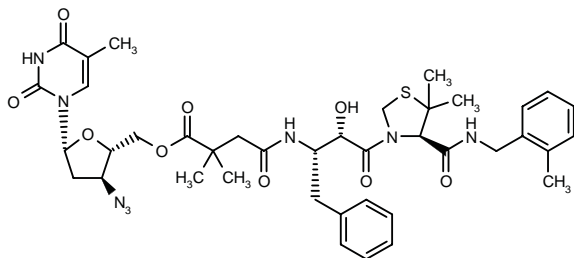
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KNI-694

300996

3'-Azido-5'-O-[3-[N-[1(S)-benzyl-2(S)-[4(R)-[N-(2-methylbenzyl)carbamoyl]-5,5-dimethylthiazolidin-3-ylcarbonyl]-2-hydroxyethyl]carbamoyl]-2,2-dimethylpropionyl]-3'-deoxythymidine



C40 H50 N8 O9 S; Mol wt: 818.9480

ACTION – Anti-HIV agent, a conjugate of an HIV protease inhibitor with the nucleoside reverse transcriptase inhibitor zidovudine with excellent antiviral activity in HIV-1_{IIIB}-infected CEM-SS cells ($EC_{50} = 0.24$ nM), where compound was 46-fold more potent than zidovudine ($EC_{50} = 11$ nM). *In vitro* stability studies showed high resistance to porcine liver esterase and high stability in human serum, but low stability in rat plasma.

SOURCE – Takeda.

REFERENCES

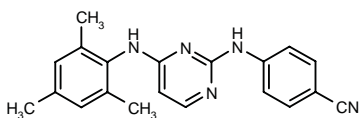
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TMC-120*

281553

4-[4-(2,4,6-Trimethylphenylamino)pyrimidin-2-ylamino]-benzonitrile

R-147681



C20 H19 N5; Mol wt: 329.4051

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor (NNRTI) with equipotent *in vitro* activity against wild-type HIV-1 and NNRTI-resistant strains encoding K103N, Y181C or G190A/S mutations ($IC_{50} = 1-10$ nM). The antiviral activity of compound was not affected by α_1 -acid glycoprotein and only slightly affected by human serum albumin. Moreover, it was fairly stable after 2-h incubation with human liver microsomes, with approximately 35% degradation. Preliminary results of phase I/II clinical studies in HIV-1-infected patients indicated that compound administered twice daily at doses of 50 and 100 mg for 7 days is safe and well tolerated.

SOURCES – Janssen; Tibotec.

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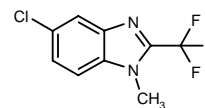
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3. De Bethune, M.P. et al. *TMC120 (R147681), a next-generation NNRTI, has potent in vitro activity against NNRTI-resistant HIV variants*. 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 304.
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5. van't Klooster, G.A.E. et al. *The novel non-nucleoside reverse transcriptase inhibitor TMC120 has potent antiretroviral activity after short-term monotherapy in treatment naïve, HIV-1 infected subjects*. Antivir Res 2001, 50(1): Abst 9.

*Identified compound **281553** (see **281551**) Drug Data Rep 2000, 022(01): 0071.

TREATMENT OF PROTOZOAL DISEASES

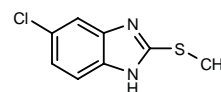
288400

5-Chloro-1-methyl-2-(trifluoromethyl)-1H-benzimidazole



C9 H6 Cl F3 N2; Mol wt: 234.6074

ACTION – Antiprotozoal agent active against *Giardia lamblia* and *Entamoeba histolytica* ($IC_{50} = 0.042$ and 0.046 μ M, respectively), as well as against *Trichinella spiralis*. Compound showed greater antiprotozoal activity than metronidazole and albendazole and comparable anthelmintic activity against *T. spiralis* to albendazole. However, unlike albendazole, compound did not inhibit tubulin polymerization even at high concentrations. Another benzimidazole derivative is:



288395: C8 H7 Cl N2 S

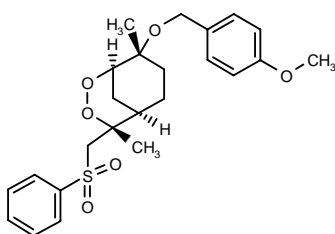
SOURCES – Universidad Nacional Autonoma de Mexico, Mexico D.F. (MX); Centro de Investigación y Estudios Avanzados, Mexico D.F. (MX); Centro Médico Nacional Siglo XXI, México D.F. (MX).

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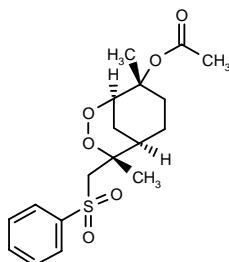
298427

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-8-(4-methoxybenzyloxy)-4-(phenylsulfonylmethyl)-2,3-dioxabicyclo[3.3.1]nonane



C24 H30 O6 S; Mol wt: 446.5610

ACTION – Antimalarial agent proven active *in vitro* against chloroquine-sensitive *Plasmodium falciparum* NF54, inhibiting the incorporation of [³H]-hypoxanthine with an IC₅₀ value of 14 nM. *In vivo*, compound was effective against chloroquine-sensitive *Plasmodium berghei* (ED₅₀ = 1.3 mg/kg s.c., ED₉₀ = 2.3 mg/kg s.c.) and chloroquine-resistant *Plasmodium yoelii* (ED₅₀ = 4.8 mg/kg s.c., ED₉₀ = 8.3 mg/kg s.c.), being similar in potency to artemisinin (ED₅₀ = 0.95 mg/kg s.c., ED₉₀ = 2.5 mg/kg s.c. against *P. berghei*, and ED₅₀ = 5.8 mg/kg s.c., ED₉₀ = 10.0 mg/kg s.c. against *P. yoelii*) and arteflene (ED₅₀ = 2.7 mg/kg s.c., ED₉₀ = 3.9 mg/kg s.c. against *P. berghei*). Another exemplified compound from this series of 2,3-dioxabicyclo[3.3.1]nonane derivatives is:



298428: C18 H24 O6 S

SOURCES – Johns Hopkins University, Baltimore, MD (US); Yeda.

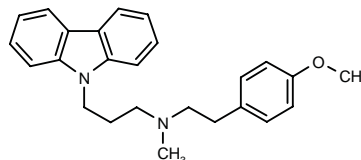
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TREATMENT OF SEPTIC SHOCK

298333

N-[3-(9*H*-Carbazol-9-yl)propyl]-*N*-[2-(4-methoxyphenyl)ethyl]-*N*-methylamine



C25 H28 N2 O; Mol wt: 372.5092

ACTION – Antiapoptotic and antiseptic agent that inhibits sphingomyelinase, potentially useful for the treatment of septicemia, arteriosclerosis, neurodegenerative diseases such as Alzheimer's disease and retroviral infections such as HIV infection. *In vitro*, compound inhibited mLDL- or recombinant TNF- α -induced apoptosis of human peripheral blood mononuclear cells with an IC₅₀ value of 0.5 μ M, as well as sphingomyelinase activity in human macrophages with an IC₅₀ value of 9 μ M. In addition, it was shown to protect against lipopolysaccharide-induced mortality in mice at 20 mg/kg i.p.

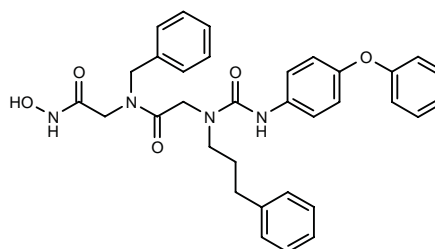
SOURCES – Friedrich-Schiller-Universität Jena, Jena (DE); Universität Heidelberg, Heidelberg (DE).

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298735

2-[*N*-Benzyl-2-[3-(4-phenoxyphenyl)-1-(3-phenylpropyl)-ureido]acetamido]acetohydroxamic acid



C33 H34 N4 O5; Mol wt: 566.6546

ACTION – A representative compound from a series of peptoids that act as inhibitors of matrix metalloproteinases (MMPs), particularly type IV collagenases such as MMP-2 (gelatinase A) and MMP-9 (gelatinase B) and are therefore expected to be useful in the treatment of septic and toxic shock, systemic inflammatory response syndrome (SIRS) and cancer. *In vitro*, compound was shown to potently and concentration-dependently inhibit MMP-2 at 10-40 µM, while exhibiting little cytotoxicity against cultured murine F442 fibroblasts at concentrations up to 100 µM. In addition, it was shown to inhibit the invasion of Matrigel by HiMel cells, giving about 50% inhibition at 10 µM.

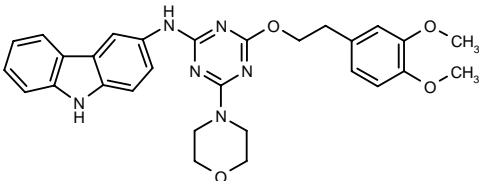
SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

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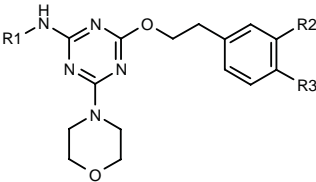
299141

N-[4-[2-(3,4-Dimethoxyphenyl)ethoxy]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-9H-carbazol-3-amine



C29 H30 N6 O4; Mol wt: 526.5940

ACTION – A compound with high potency in inhibiting the production of IL-12, potentially useful for the treatment of sepsis and autoimmune disorders such as rheumatoid arthritis, Crohn’s disease, psoriasis and multiple sclerosis. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
299142	4-(2-MeO-PhNH)-Ph	OMe	OMe	C ₃₀ H ₃₄ N ₆ O ₅
299143	3-indolyl-CH=N	OMe	OH	C ₂₅ H ₂₇ N ₇ O ₄
299144	1-Me-3-indolyl-CH=CH	H	H	C ₂₆ H ₂₈ N ₆ O ₂

SOURCE – Shionogi.

REFERENCES

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DROTRECOGIN ALFA (ACTIVATED)

275685

Recombinant human activated protein C

LY-203638
rhAPC
Zovant™ (former brand name)
Xigris™

ACTION – Recombinant human activated protein C that possesses antithrombotic, antiinflammatory and profibrinolytic properties. Phase III clinical studies in patients with severe sepsis showed that compound at a dose of 24 µg/kg/h i.v. for 96 h significantly reduced mortality and appears to have an acceptable risk–benefit profile. It is undergoing review by regulatory authorities in the US, Europe, Australia and Canada for the treatment of sepsis with associated acute organ dysfunction.

SOURCE – Lilly.

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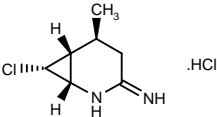
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MONOGRAPH – Sorbera, L.A. et al. *Drotrecogin alfa (activated)*. Drugs Fut 2001, 26(5): 440.

ONO-1714*

269542

(+)-(1*S*,5*S*,6*R*,7*R*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-imine hydrochloride



C7 H11 Cl N2 . HCl ; Mol wt: 195.0918

ACTION – Potent and selective inhibitor of inducible nitric oxide synthase (iNOS) with a K_i of 1.88 nM against human enzyme and 10-fold selectivity over human endothelial NOS (eNOS); when compared with L-NMMA and aminoguanidine, compound was 451- and > 20,000-fold more potent, respectively, against iNOS and 33.9- and 16.1-fold more selective for iNOS versus eNOS. Compound inhibited nitrite accumulation in RAW264.7 cells stimulated with lipopolysaccharide (LPS; IC_{50} = 20 nM) and it decreased the LPS-induced plasma nitrate/nitrite accumulation in mice in a dose-dependent manner, with an ID_{50} of 0.010 mg/kg s.c., being 2,600-fold more potent than L-NMMA. In a model of ulcerative colitis in mice treated with dextran sulfate sodium, compound at doses of 0.03-0.3 mg/kg i.p. attenuated colonic inflammation and injury, as well as increases in serum and colonic lumen nitrate and nitrite levels. In this model, it also inhibited peroxynitrite formation and lipid peroxidation and decreased levels of inflammatory cytokines in colonic mucosa, as well as mRNA expression of iNOS in colonic tissue. In a model of sepsis induced by cecal ligation and puncture in rats, compound given at a dose of 0.03 mg/kg every 12 h induced a significant reduction in plasma NO levels and improved survival. Compound is in phase I trials for the treatment of sepsis and may have potential in the treatment of inflammatory bowel disease.

SOURCE – Ono.

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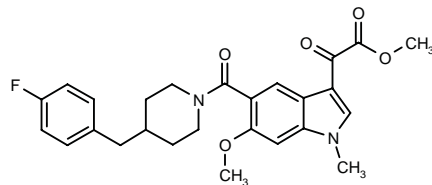
*Identified compound **269542** Drug Data Rep 1998, 020(11): 0978.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

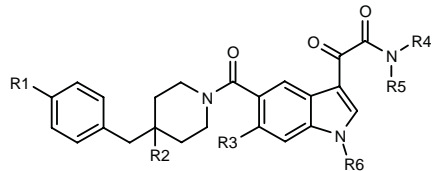
297947

2-[5-[4-(4-Fluorobenzyl)piperidin-1-ylcarbonyl]-6-methoxy-1-methyl-1*H*-indol-3-yl]-2-oxoacetic acid methyl ester

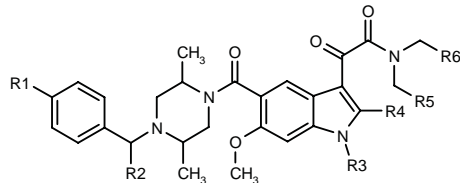


C26 H27 F N2 O5; Mol wt: 466.5063

ACTION – p38α kinase inhibitor (IC₅₀ = 0.1-1.5 μM), potentially useful for the treatment of inflammatory or proliferative disorders, i.e., multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, septic shock, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, psoriasis, restenosis, bone resorption disorders, graft-versus-host reaction, Crohn’s disease, ulcerative colitis, as well as certain cardiovascular disorders and Alzheimer’s disease. Other exemplified indole-type compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
297948	F	H	Cl		-CH2CH2OCH2CH2-	Me	C ₂₈ H ₂₉ ClFN ₃ O ₄
297949	F	H	Cl	Me	Me	CN	C ₂₆ H ₂₄ ClFN ₄ O ₃
297952	F	H	Cl	Me	Et	Me	C ₂₇ H ₂₉ ClFN ₃ O ₃
297954	H	H	OMe		-CH2CH2N(Me)CH2CH2-	H	C ₂₉ H ₃₄ N ₄ O ₄
297956	F	H	OMe	H	CH2CH(OH)CH2OH	H	C ₂₇ H ₃₀ FN ₃ O ₆
297959	F	F	OMe	Me	Me	H	C ₂₆ H ₂₇ F ₂ N ₃ O ₄



Compound	R1	R2	R3	R4	R5	R6	Isomer	Formula
297950	F	H	Ac	Me	H	H	2R,5S	C ₃₀ H ₃₅ FN ₄ O ₅
297953	F	H	Me	H	-CH2OCH2-		2R,5S	C ₃₀ H ₃₅ FN ₄ O ₅
297957	H	Me	H	H	H	H		C ₂₈ H ₃₄ N ₄ O ₄

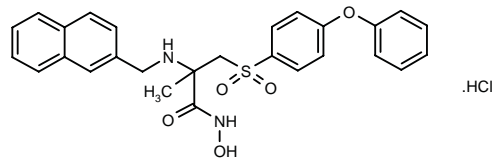
SOURCE – Scios.

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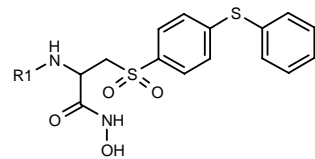
297971

2-Methyl-2-(2-naphthalenylmethylamino)-3-[4-(phenoxy)phenylsulfonyl]propionohydroxamic acid hydrochloride



C27 H26 N2 O5 S . HCl; Mol wt: 527.0383

ACTION – Matrix metalloprotease inhibitor, particularly active against MMP-2 (gelatinase A; IC₅₀ = 0.4 nM), MMP-9 (gelatinase B) and MMP-13 (collagenase 3; IC₅₀ = 1.4 nM) with little or no activity against MMP-1 (fibroblast collagenase; IC₅₀ > 10,000 nM). Potential uses of this compound include the treatment of rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulcer, tumor metastasis, angiogenesis, periodontal disease, proteinuria, Alzheimer’s disease, coronary thrombosis, plaque formation and bone disease. Other exemplified α-amino-β-sulfonyl hydrox-amic acids include the following:



Compound	R1	Isomer	Formula
297972	N-(PhCH2OCO)-Gly-		C ₂₆ H ₂₅ N ₃ O ₇ S ₂
297973	N-(PhCH2OCO)-L-Ala-	R	C ₂₆ H ₂₇ N ₃ O ₇ S ₂
297974	4-Pyr-CO		C ₂₁ H ₁₉ N ₃ O ₅ S ₂

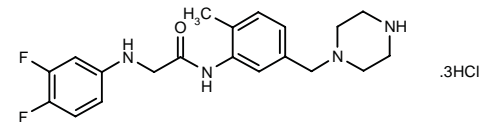
SOURCE – Pharmacia.

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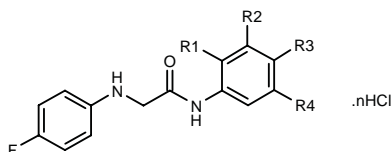
298009

2-(3,4-Difluorophenylamino)-*N*-[2-methyl-5-(1-piperazinylmethyl)phenyl]acetamide trihydrochloride

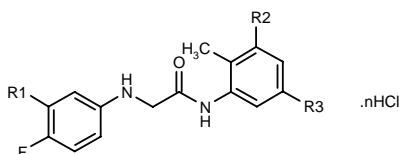


C20 H24 F2 N4 O . 3HCl; Mol wt: 483.8153

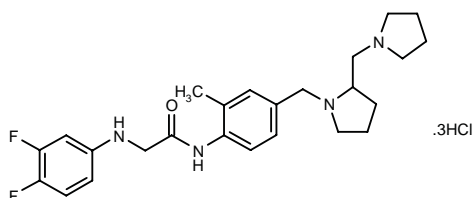
ACTION – Immunosuppressant that acts via inhibition of the P2X₇ receptor. Potentially useful for the treatment of rheumatoid arthritis, asthma and chronic obstructive pulmonary disease. Other specifically claimed substituted phenyl derivatives include the following:



Compound	R1	R2	R3	R4	n	Formula
298011	Cl	H	H	1-Piz-CH2	3	C ₁₉ H ₂₁ ClF ₂ N ₄ O.3HCl
298022	H	H	Me	CONHCH2CH2N(Me)2	0	C ₂₀ H ₂₄ F ₂ N ₄ O ₂



Compound	R1	R2	R3	n	Formula
298019	Cl	H	4-Pip-O	2	C ₂₀ H ₂₃ FN ₃ O ₂ .2HCl
298020	F	H	1-Piz	3	C ₁₉ H ₂₂ F ₂ N ₄ O.3HCl
298021	F	H	2(S)-(CH2OH)- -1-pyrrolidinyl-CH2	0	C ₂₁ H ₂₈ F ₂ N ₃ O ₂
298023	F	CH2N(Me)2	H	0	C ₁₈ H ₂₁ F ₂ N ₃ O



298018: C₂₅ H₃₂ F₂ N₄ O . 3HCl

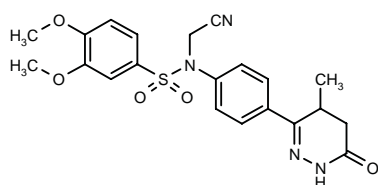
SOURCE – AstraZeneca.

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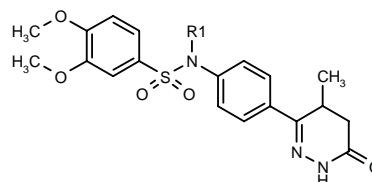
298068

N-(Cyanomethyl)-3,4-dimethoxy-*N*-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]benzenesulfonamide



C₂₁ H₂₂ N₄ O₅ S; Mol wt: 442.4938

ACTION – Agent for the treatment or prevention of inflammatory, allergic and immunological disorders, ischemic vascular disorders, sepsis, cachexia, viral diseases, type 2 diabetes and diabetic complications. The compound acts as an inhibitor of the production of TNF- α , as demonstrated *in vitro* in lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (IC₅₀ = 2.0 μ M) and in 3T3-L1 cells (41% inhibition at 10 μ M), and *in vivo* in LPS-stimulated mice (54.7% inhibition at 30 mg/kg p.o.). Compound was further shown to decrease blood glucose levels in diabetic KKA^y/Ta mice at 200 mg/kg/day p.o. x 10 days and to reduce the arthritis score in a murine model of bovine type 2 collagen-induced arthritis at 30 mg/kg/day p.o. x 5 doses/week x 4 weeks. Other compounds from this series of dihydropyridazinone derivatives include the following:



Compound	R1	Formula
298069	H	C ₁₉ H ₂₁ N ₃ O ₅ S
298070	Me	C ₂₀ H ₂₃ N ₃ O ₅ S
298071	Pr	C ₂₂ H ₂₇ N ₃ O ₅ S
298072	ethynyl-CH2	C ₂₂ H ₂₃ N ₃ O ₅ S

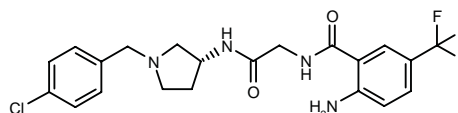
SOURCE – Mitsui Chemicals.

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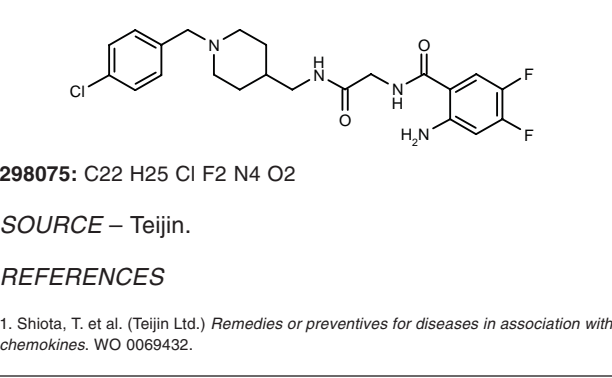
298074

2-Amino-*N*-[*N*-[1-(4-chlorobenzyl)pyrrolidin-3-yl]-carbamoylmethyl]-4-(trifluoromethyl)benzamide



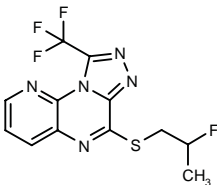
C₂₁ H₂₂ Cl F₃ N₄ O₂; Mol wt: 454.8778

ACTION – Agent for the treatment of rheumatoid arthritis, atherosclerosis, psoriasis, asthma, ulcerative colitis, nephritis, multiple sclerosis, pulmonary fibrosis, congestive heart failure and cardiomyopathy that acts by inhibiting the action of chemokines such as macrophage inflammatory protein-1 α (MIP-1 α) and monocyte chemoattractant protein-1 (MCP-1) on target cells. *In vitro*, compound was shown to inhibit the binding of human MIP-1 α and MCP-1 to human monocytic leukemia THP-1 cells, producing 20-50% inhibition at 2 μ M and > 80% inhibition at 1 μ M, respectively. In addition, it inhibited MCP-1-induced chemotaxis of THP-1 cells with an IC₅₀ value of 0.1 μ M or less. *In vivo*, compound significantly inhibited collagen-induced arthritis in the rat at 100 mg/kg/day p.o. x 12 weeks and was effective in a rat model of nephritis, significantly reducing proteinuria and serum creatinine levels at 100 mg/kg p.o. b.i.d. Another exemplified compound within this broad series of cyclic amine derivatives is:



298270

6-(2-Fluoropropylsulfanyl)-9-(trifluoromethyl)pyrido[3,2-e]-[1,2,4]triazolo[4,3-a]pyrazine



C12 H9 F4 N5 S; Mol wt: 331.2961

ACTION – An inhibitor of adhesion molecule expression shown to inhibit E-selectin, VCAM-1 and ICAM-1 expression in stimulated human umbilical vein endothelial cells (HUVEC) with respective IC₅₀ values of 0.10, 0.06 and 0.09 μM. Potentially useful in the treatment and/or prevention of inflammatory disorders including rheumatoid arthritis, allergies, bronchial asthma, atopic dermatitis, psoriasis, ischemia–reperfusion disorders, nephritis, hepatitis, multiple sclerosis, ulcerative colitis, acute respiratory distress syndrome, transplant rejection and sepsis, as well as diabetes, autoimmune diseases, cancer metastasis, arteriosclerosis and AIDS. A representative compound from a series of condensed pyrazine derivatives.

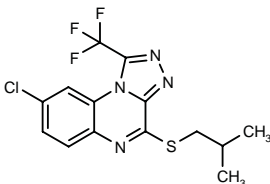
SOURCE – Ono.

REFERENCES

1. Kobayashi, K. et al. (Ono Pharmaceutical Co., Ltd.) *Condensed pyrazine cpds. and medicines containing them as active ingredient*. JP 2000319278.

298271

8-Chloro-4-(isobutylsulfanyl)-1-(trifluoromethyl)[1,2,4]-triazolo[4,3-a]quinoxaline



C14 H12 Cl F3 N4 S; Mol wt: 360.7898

ACTION – An inhibitor of adhesion molecule expression shown to inhibit E-selectin, VCAM-1 and ICAM-1 expression in stimulated human umbilical vein endothelial cells (HUVEC) with respective IC₅₀ values of 0.14, 0.07 and 0.08 μM. Potentially useful in the treatment and/or prevention of inflammatory disorders including rheumatoid arthritis, allergies, bronchial asthma, atopic dermatitis, psoriasis, ischemia–reperfusion disorders, nephritis, hepatitis, multiple sclerosis, ulcerative colitis, acute respiratory distress syndrome, transplant rejection and sepsis, as well as diabetes, autoimmune diseases, cancer metastasis, arteriosclerosis and AIDS. A representative compound from a series of condensed pyrazine derivatives.

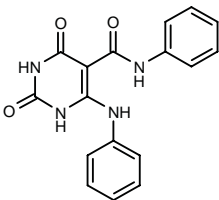
SOURCE – Ono.

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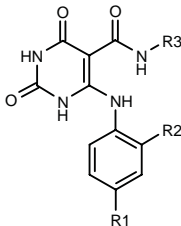
298624

2,4-Dioxo-N-phenyl-6-(phenylamino)-1,2,3,4-tetrahydropyrimidine-5-carboxamide



C17 H14 N4 O3; Mol wt: 322.3226

ACTION – An inhibitor of c-Jun N-terminal kinases (JNK), especially JNK3 (also known as SAPK1b; K_i < 1 μM), with potential for the treatment or prevention of inflammatory and autoimmune diseases, destructive bone disorders, proliferative and neurodegenerative diseases, infectious diseases, allergies, ischemia–reperfusion injury, heart attack, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy and thrombin-induced platelet aggregation. Other exemplified compounds from this series of 2,4-dioxo-1,2,3,4-tetrahydropyrimidine derivatives include the following:



Compound	R1	R2	R3	Formula
298626	H	H	2-Pyr	C ₁₆ H ₁₃ N ₅ O ₃
298627	H	H	4-F-Ph	C ₁₇ H ₁₃ FN ₄ O ₃
298628	H	H	3-Me-Ph	C ₁₈ H ₁₆ N ₄ O ₃
298631	H	Me	Ph	C ₁₈ H ₁₆ N ₄ O ₃
298632	H	Me	4-F-Ph	C ₁₈ H ₁₅ FN ₄ O ₃
298634	H	Me	3-Me-Ph	C ₁₉ H ₁₈ N ₄ O ₃
298635	F	H	Ph	C ₁₇ H ₁₃ FN ₄ O ₃
298636	F	H	4-F-Ph	C ₁₇ H ₁₂ F ₂ N ₄ O ₃
298638	F	H	3-Me-Ph	C ₁₈ H ₁₅ FN ₄ O ₃

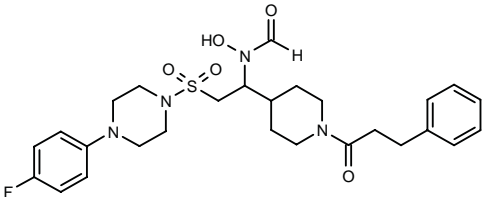
SOURCE – Vertex.

REFERENCES

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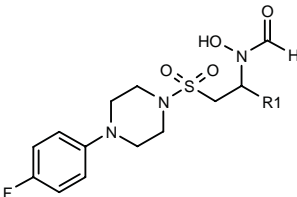
298640

N-[2-[4-(4-Fluorophenyl)piperazin-1-ylsulfonyl]-1-[1-(3-phenylpropionyl)piperidin-4-yl]ethyl]-N-hydroxyformamide



C27 H35 F N4 O5 S; Mol wt: 546.6605

ACTION – Matrix metalloprotease inhibitor, especially active against MMP-13 (collagenase 3), potentially useful for the treatment of arthritis and atherosclerosis. Other exemplified compounds include the following:



Compound	R1	Formula
298642	1-(4-Cl-PhOCH2CO)-4-Pip	C ₂₆ H ₃₂ ClFN ₄ O ₆ S
298643	1-Ac-4-Pip	C ₂₀ H ₂₉ FN ₄ O ₅ S
298644	1-(PrSO2)-4-Pip	C ₂₁ H ₃₃ FN ₄ O ₆ S ₂
298645	1-(PhNHCO)-4-Pip	C ₂₅ H ₃₂ FN ₅ O ₅ S
298646	1-(3-CF3-PhSO2)-4-Pip	C ₂₅ H ₃₀ F ₄ N ₄ O ₆ S ₂
298647	1-(2-thienyl-SO2)-4-Pip	C ₂₂ H ₂₉ FN ₄ O ₆ S ₃
298648	1-(PhCH2NHCO)-4-Pip	C ₂₆ H ₃₄ FN ₅ O ₅ S
298649	1-(i-PrNHCO)-4-Pip	C ₂₂ H ₃₄ FN ₅ O ₅ S
298650	1-(MeSO2)-3-Pip	C ₁₉ H ₂₉ FN ₄ O ₆ S ₂
298651	1-(2-Cl-PhSO2)-3-Pip	C ₂₄ H ₃₀ ClFN ₄ O ₆ S ₂
298652	1-(5-Br-2-thienyl-SO2)-3-Pip	C ₂₂ H ₂₈ BrFN ₄ O ₆ S ₃
298654	1-(i-PrSO2)-3-Pip	C ₂₁ H ₃₃ FN ₄ O ₆ S ₂
298656	1-(PhCH2CH2NHCO)-3-Pip	C ₂₇ H ₃₆ FN ₅ O ₅ S

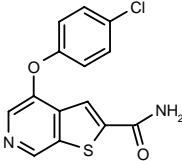
SOURCE – AstraZeneca.

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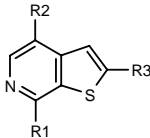
298641

4-(4-Chlorophenoxy)thieno[2,3-c]pyridine-2-carboxamide



C14 H9 Cl N2 O2 S; Mol wt: 304.7561

ACTION – Cell adhesion inhibitor that inhibits E-selectin and ICAM-1 (82 and 74% inhibition, respectively, of TNF-α-induced E-selectin and ICAM-1 expression in human umbilical vein endothelial cells [HUVEC] at 1 μM) with selectivity over VCAM-1 (50% inhibition at 1 μM in HUVEC). Potentially useful for the treatment or prevention of diseases caused by the expression of adhesion molecules including diseases where leukocyte trafficking plays a role such as acute and chronic inflammatory diseases, autoimmune diseases, tumor metastasis, allograft rejection and reperfusion injury. Other exemplified bicyclic compounds include the following:



Compound	R1	R2	R3	Formula
298653	H	4-Me-PhS	CH=CHCONH2	C ₁₇ H ₁₄ N ₂ O ₂ S
298655	H	4-Me-PhO	CONH2	C ₁₅ H ₁₂ N ₂ O ₂ S
298657	H	4-CF3-Ph	CONH2	C ₁₅ H ₉ F ₃ N ₂ OS
298658	H	4-Cl-PhO	CON(Me)2	C ₁₆ H ₁₃ ClN ₂ O ₂ S
298659	H	4-Cl-PhO	SO2NH2	C ₁₃ H ₉ ClN ₂ O ₃ S ₂
298660	H	4-CN-PhO	CONH2	C ₁₅ H ₉ N ₃ O ₂ S
298940	H	4-Ac-PhO	CONHMe	C ₁₇ H ₁₄ N ₂ O ₃ S
298941	H	4-[1-[EtO(CH2CH2O)2CH2]-cyclopropyl]-PhO	CONHMe	C ₂₅ H ₃₀ N ₂ O ₅ S
298942	H	4-Cl-PhCO	CONHMe	C ₁₆ H ₁₁ ClN ₂ O ₂ S
298943	Cl	4-Cl-PhO	CONH2	C ₁₄ H ₈ Cl ₂ N ₂ O ₂ S

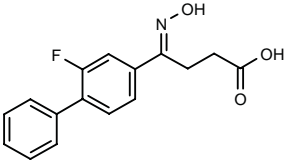
SOURCE – Abbott.

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1. Arendsen, D.L. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory cpds*. WO 0075145.

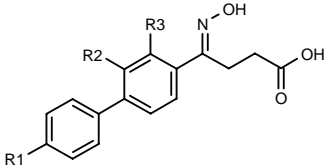
298738

4-(2-Fluorobiphenyl-4-yl)-4-(hydroxyimino)butyric acid



C16 H14 F N O3; Mol wt: 287.2886

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly gelatinase A (MMP-2), stromelysin 1 (MMP-3) and collagenase 3 (MMP-13), potentially useful for the treatment of atherosclerotic plaque rupture, aortic aneurysm, heart failure, restenosis, periodontal disease, corneal ulceration, burns, decubital ulcers, wounds, cancer, arthritis, autoimmune or inflammatory disorders, multiple sclerosis, pain, neurodegenerative disorders and renal diseases. Other specifically claimed compounds from this series of fluorine-substituted biphenyl butyric acids include the following:



Compound	R1	R2	R3	Formula
298739	H	H	F	C ₁₆ H ₁₄ FNO ₃
298740	Cl	F	H	C ₁₆ H ₁₃ ClFNO ₃
298741	Cl	H	F	C ₁₆ H ₁₃ ClFNO ₃

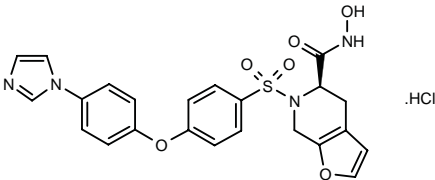
SOURCE – Pfizer.

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1. Purchase C.F. Jr. et al. (Pfizer Inc.) *Fluorine-substd. biphenyl butyric acids and their derivs. as inhibitors of matrix metalloproteinases*. US 6169103.

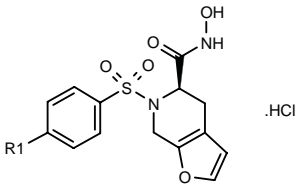
298743

6-[4-[4-(1*H*-Imidazol-1-yl)phenoxy]phenylsulfonyl]-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-5(*R*)-carboxylic acid hydrochloride



C23 H20 N4 O6 S . HCl; Mol wt: 516.9599

ACTION – An inhibitor of matrix metalloproteinases (MMPs) reported to inhibit human gelatinase A (MMP-2), stromelysin 1 (MMP-3), neutrophil collagenase (MMP-8), gelatinase B (MMP-9) and collagenase 3 (MMP-13) with IC₅₀ values in the range 0.1-10 nM and to exhibit 1,000-fold selectivity for MMP-8 and MMP-13 relative to human fibroblast collagenase (MMP-1). Compound gave 82 and 83% protection, respectively, against collagen and proteoglycan degradation at 0.1 μM and inhibited collagen-induced neovascularization in rat thoracic aorta with an IC₅₀ value of 2.3 nM. *In vivo*, it inhibited MMP-13 in mice following administration of 30 mg/kg p.o. with a good duration of action (88, 83 and 51% inhibition, respectively, at 30 min, 2 h and 8 h postadministration), and was found to be active in an adjuvant-induced arthritis model in the rat, giving a 42% reduction in femoral mineral content loss, as well as 61 and 98% reductions, respectively, in glycosaminoglycan and hydroxyproline loss from articular cartilage when given at 40 mg/kg p.o. b.i.d. Other specifically claimed compounds from this series of 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine derivatives are:



Compound	R1	Formula
298744	4-(1-pyrrolidinyl-CH2CH2O)-Ph	C ₂₆ H ₂₉ N ₃ O ₆ S.HCl
298745	4-(4H-1,2,4-triazol-4-yl)-PhO	C ₂₂ H ₁₉ N ₅ O ₆ S.HCl
298746	4-(4-Pyr)-PhO	C ₂₅ H ₂₁ N ₃ O ₆ S.HCl
298747	4-(4H-1,2,4-triazol-4-yl)-PhS	C ₂₂ H ₁₉ N ₅ O ₅ S ₂ .HCl

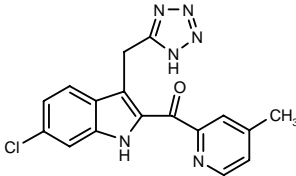
SOURCE – ADIR.

REFERENCES

1. de Nanteuil, G. et al. (ADIR et Cie.) *Metalloprotease inhibitors, process for their preparation and pharmaceutical compsns. containing them*. EP 1065209, FR 2795730, JP 2001039983.

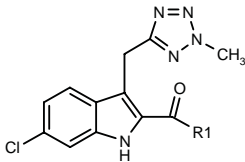
298748

1-[6-Chloro-3-(1*H*-tetrazol-5-ylmethyl)-1*H*-indol-2-yl]-1-(4-methylpyridin-2-yl)methanone

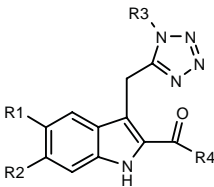


C17 H13 Cl N6 O; Mol wt: 352.7837

ACTION – Cyclooxygenase inhibitor with selectivity for COX-2, useful for the treatment or alleviation of pain, inflammation and inflammation-associated conditions such as arthritis. Other specifically claimed tetrazolylalkyl indole derivatives include the following:



Compound	R1	Formula
298749	4-Me-2-Pyr	C ₁₈ H ₁₅ ClN ₆ O
298758	5-Me-2-thienyl	C ₁₇ H ₁₄ ClN ₅ OS



Compound	R1	R2	R3	R4	Formula
298750	H	Cl	Me	4-Me-2-Pyr	C ₁₈ H ₁₅ ClN ₆ O
298751	H	Cl	H	5-Me-2-Pyr	C ₁₇ H ₁₃ ClN ₆ O
298752	H	Cl	H	4-Et-2-Pyr	C ₁₈ H ₁₅ ClN ₆ O
298753	H	Cl	H	4-Cl-2-Pyr	C ₁₆ H ₁₀ Cl ₂ N ₆ O
298754	H	Cl	H	5-Cl-2-Pyr	C ₁₆ H ₁₀ Cl ₂ N ₆ O
298755	H	Cl	H	4-MeO-2-Pyr	C ₁₇ H ₁₃ ClN ₆ O ₂
298756	H	Cl	H	5-Me-2-thienyl	C ₁₆ H ₁₂ ClN ₅ OS
298757	H	Cl	Me	5-Me-2-thienyl	C ₁₇ H ₁₄ ClN ₅ OS
298759	H	Cl	H	3-isoquinoliny	C ₂₀ H ₁₃ ClN ₆ O
298760	H	CF ₃	H	3-isoquinoliny	C ₂₁ H ₁₃ F ₃ N ₆ O
298761	CF ₃	H	H	4-Me-2-Pyr	C ₁₈ H ₁₃ F ₃ N ₆ O
298762	F	H	H	4-Me-2-Pyr	C ₁₇ H ₁₃ FN ₆ O
298763	H	F	H	4-Me-2-Pyr	C ₁₇ H ₁₃ FN ₆ O

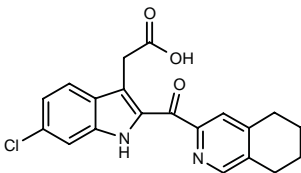
SOURCE – Pfizer.

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1. Nakao, K. and Stevens, R.W. (Pfizer Inc.) *Tetrazolylalkyl indole cpds. as anti-inflammatory and analgesic agents*. EP 1065206, JP 2001031676.

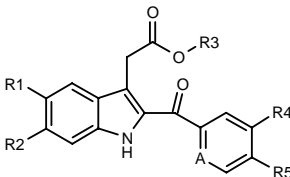
298764

2-[6-Chloro-2-(5,6,7,8-tetrahydroisoquinolin-3-ylcarbonyl)-1H-indol-3-yl]acetic acid



C20 H17 Cl N2 O3; Mol wt: 368.8183

ACTION – Cyclooxygenase inhibitor with selectivity for COX-2, useful for the treatment or alleviation of pain, inflammation and inflammation-associated conditions such as arthritis. Other specifically claimed bicyclic carbonyl indole derivatives include the following:



Compound	R1	R2	R3	R4,R5	A	Formula
298765	H	Cl	H	-OCH2CH2O-	CH	C ₁₉ H ₁₄ ClNO ₅
298766	CF ₃	H	H	-OCH2CH2O-	CH	C ₂₀ H ₁₄ F ₃ NO ₅
298767	H	Cl	H	-CH2CH2O-	CH	C ₁₉ H ₁₄ ClNO ₄
298768	H	Cl	Me	-(CH2)4-	N	C ₂₁ H ₁₉ ClN ₂ O ₃
298769	H	Cl	Me	-OCH2CH2O-	CH	C ₂₀ H ₁₆ ClNO ₅
298770	CF ₃	H	Me	-OCH2CH2O-	CH	C ₂₁ H ₁₆ F ₃ NO ₅
298771	H	Cl	Me	-CH2CH2O-	CH	C ₂₀ H ₁₆ ClNO ₄

Compound	R1	R2	R3	R4,R5	A	Formula
298772	H	Cl	Me	-OCH2O-	CH	C ₁₉ H ₁₄ ClNO ₅
298774	Cl	Cl	Me	-(CH2)3-	CH	C ₂₁ H ₁₇ Cl ₂ NO ₃
298775	H	Cl	Me	-CH2N(Me)CH2CH2-	CH	C ₂₂ H ₂₁ ClN ₂ O ₃

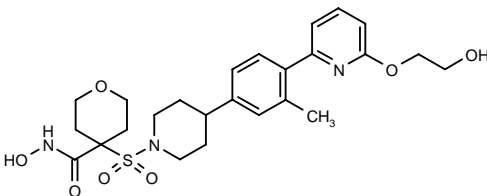
SOURCE – Pfizer.

REFERENCES

1. Hayashi, S. et al. (Pfizer Inc.) *Bicycliccarbonyl indole cpds. as anti-inflammatory/analgesic agents and as COX-2 inhibitors*. EP 1065204, JP 2001031677.

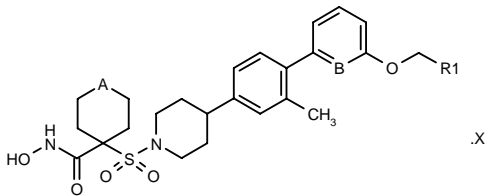
298808

4-[4-[4-[6-(2-Hydroxyethoxy)pyridin-2-yl]-3-methylphenyl]-piperidin-1-ylsulfonyl]tetrahydropyran-4-carbohydroxamic acid



C25 H33 N3 O7 S; Mol wt: 519.6157

ACTION – Matrix metalloproteinase (MMP) inhibitor that acts as a potent inhibitor of MMP-3 (stromelysin 1; IC₅₀ < 10 nM) and shows selectivity over other MMPs such as MMP-1 (fibroblast collagenase; IC₅₀ > 1000 nM), MMP-2 (gelatinase A; IC₅₀ > 100 nM), MMP-9 (gelatinase B; IC₅₀ > 70 nM) and MMP-14 (MT-1 MMP; IC₅₀ > 2000 nM). Potentially useful for the treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wounds, skin diseases, cancer metastasis, tumor angiogenesis, age-related macular degeneration, fibrotic diseases, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells. Other exemplified hydroxamic acid derivatives include the following:



Compound	R1	A	B	X	Formula
298809	(S)-CH(OH)CH2OH	O	N		C ₂₈ H ₃₅ N ₃ O ₈ S
298810	(R)-CH(OH)CH2OH	O	N		C ₂₈ H ₃₅ N ₃ O ₈ S
298811	CH2OH	NH	N		C ₂₅ H ₃₄ N ₄ O ₆ S
298812	CH2OH	N(Me)	N		C ₂₆ H ₃₆ N ₄ O ₆ S
298813	(S)-CH(OH)CH2OH	O	CH		C ₂₇ H ₃₆ N ₂ O ₈ S
298814	CH2NH2	O	CH	HCl	C ₂₈ H ₃₅ N ₃ O ₆ S.HCl

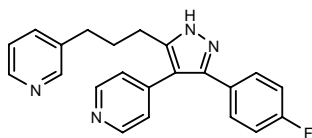
SOURCE – Pfizer.

REFERENCES

1. Dack, K.N. et al. (Pfizer Ltd.;Pfizer Inc.) *Metalloprotease inhibitors*. WO 0074681.

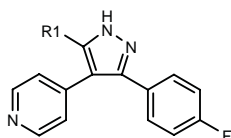
298925

3-(4-Fluorophenyl)-4-(4-pyridyl)-5-[3-(3-pyridyl)propyl]-1*H*-pyrazole



C22 H19 F N4; Mol wt: 358.4181

ACTION – Potent p38 MAP kinase inhibitor (IC_{50} = 0.0115 pM in THP-1 cells), potentially useful for the treatment of diseases mediated by TNF- α , IL-1, IL-6 or COX-2 such as arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, septic shock, asthma, HIV, cachexia, etc. Other exemplified compounds from this series of substituted pyrazole derivatives include the following:



Compound	R1	Formula
298926	3-Pyr-CH2C(Me)=CH	C ₂₃ H ₁₉ FN ₄
298927	3-Pyr-CH2CH(Me)CH2	C ₂₃ H ₂₁ FN ₄

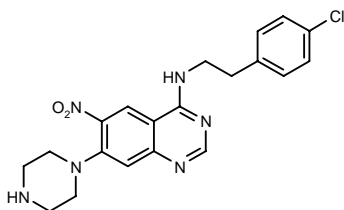
SOURCE – Teikoku Hormone.

REFERENCES

1. Minami, N. et al. (Teikoku Hormone Manufacturing Co., Ltd.) *Subst. pyrazole cpds.* WO 0075131.

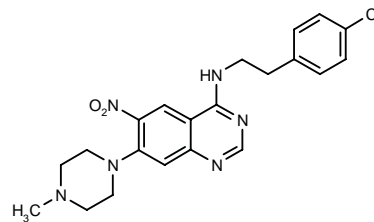
300468

N-[2-(4-Chlorophenyl)ethyl]-6-nitro-7-(1-piperazinyl)quinazolin-4-amine



C20 H21 Cl N6 O2; Mol wt: 412.8789

ACTION – Dual inhibitor of TNF- α production and T-cell proliferation (IC_{50} = 0.8 and 1.1 μ M for inhibition of lipopolysaccharide-induced TNF- α production in peripheral blood mononuclear cells [PBMCs] and concanavalin A-induced T-cell proliferation, respectively), with no cytotoxicity against PBMCs at pharmacologically active concentrations. Potentially useful as an antiinflammatory agent. Another 4-chlorophenethylaminoquinazoline derivative is:



301419: C21 H23 Cl N6 O2

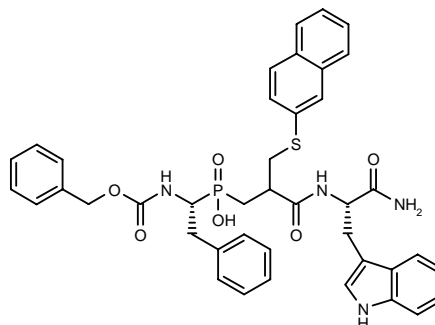
SOURCE – Japan Energy.

REFERENCES

1. Tobe, M. et al. *Structure-activity relationships of quinazoline derivatives: Dual-acting compounds with inhibitory activities toward both TNF- α production and T cell proliferation.* Bioorg Med Chem Lett 2001, 11(4): 545.

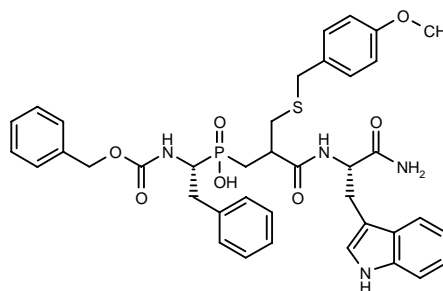
301351

*N*²-[[3-[1(*R*)-(Benzyloxycarbonylamino)-2-phenylethyl]-(hydroxy)phosphoryl]-2-(2-naphthylsulfanylmethyl)-propionyl]-L-tryptophanamide



C41 H41 N4 O6 P S; Mol wt: 748.8369

ACTION – Highly potent and selective matrix metalloproteinase (MMP-8, human neutrophil collagenase) inhibitor (K_i = 3 nM) with 30-150-fold selectivity over MMP-2 (gelatinase A; IC_{50} = 100 nM) and MMP-9 (gelatinase B; IC_{50} = 500 nM). Potentially useful as antiarthritic agent. Another related compound within this series of phosphinic peptide inhibitors is:



301350: C39 H43 N4 O7 P S

SOURCE – University of Athens, Athens (GR).

REFERENCES

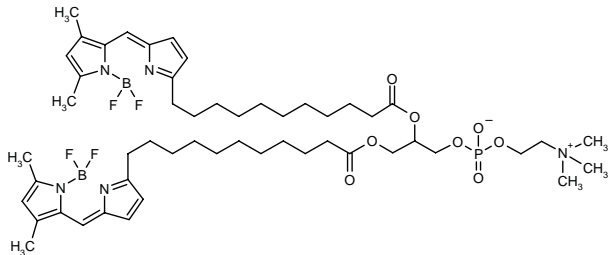
1. Matziari, M. et al. *Convenient synthesis and diversification of dehydroalaninyl phosphinic peptide analogues.* Org Lett 2001, 3(5): 659.

D-3862

301189

[μ-[20-[5-[(3,5-Dimethyl-2*H*-pyrrol-2-ylidene-κ*N*)methyl]-1*H*-pyrrol-2-yl-κ*N*]-7-[11-[5-[(3,5-dimethyl-2*H*-pyrrol-2-ylidene-κ*N*)methyl]-1*H*-pyrrol-2-yl-κ*N*]-1-oxoundecyloxy]-4-hydroxy-*N,N,N*-trimethyl-10-oxo-3,5,9-trioxa-4-phosphaeicosan-1-aminium 4-oxidato(3-)]]tetrafluorodiboron

Bis-BODIPYFLC₁₁-PC



C52 H78 B2 F4 N5 O8 P; Mol wt: 1029.8030

ACTION – Potent cytosolic phospholipase A₂ (cPLA₂) inhibitor with significant antiinflammatory activity in a model of phorbol ester-induced edema in mice, where indomethacin showed less activity and higher toxicity. Potentially useful as an antiinflammatory agent.

SOURCE – Nippon Soda.

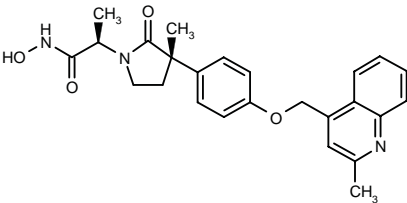
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1. Kubota-Takagi, M. et al. *Screening of novel potent IV α-cytosolic phospholipase A2 inhibitors and the antiinflammatory activities.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-261.

IK-682

301688

2(*R*)-[3(*S*)-Methyl-3-[4-(2-methylquinolin-4-ylmethoxy)-phenyl]-2-oxopyrrolidin-1-yl]propionohydroxamic acid



C25 H27 N3 O4; Mol wt: 447.5321

ACTION – Nonpeptide inhibitor of TNF-α-converting enzyme (TACE) with good *in vivo* antiinflammatory properties. Potentially useful for the treatment of rheumatoid arthritis and inflammatory bowel disease.

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Decicco, C.P. *Rational design and therapeutic application of metalloproteinase inhibitors of TNF-α.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 189.

MAb AJH10

298429

Monoclonal antibody that binds an epitope of VLA-1

ACTION – Anti-integrin monoclonal antibody, targeted particularly to the α₁-integrin subunit, that blocks the interaction of proinflammatory leukocytes with components of the extracellular matrix such as collagen, laminin or fibronectin and is thus expected to be useful for the treatment of inflammatory disorders, particularly arthritis. Its activity was demonstrated in several models of experimental arthritis.

SOURCE – Biogen.

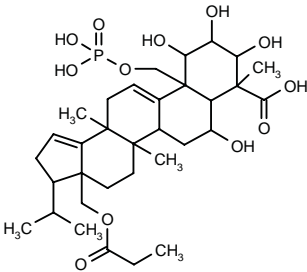
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MK-13089A

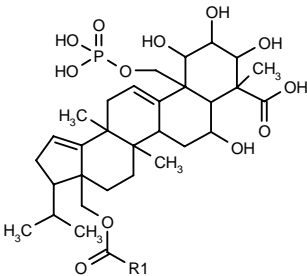
298413

7,9,10,11-Tetrahydroxy-3-isopropyl-5a,8,13a-trimethyl-11a-(phosphonooxymethyl)-3a-(propanoyloxymethyl)-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,13,13a-hexadecahydro-2*H*-cyclopenta[*a*]chrysene-8-carboxylic acid



C33 H51 O12 P; Mol wt: 670.7279

ACTION – Antiinflammatory agent isolated from *Chaetomium brasiliense* D4532 (FERM P-17362) that acts by inhibiting the expression of sialyl Lewis X (sLe^x) on the surface of leukocytes. Other triterpene derivatives isolated from the same source are:



Compound	R1	Formula
MK-13089B [298414]	Pr	C ₃₄ H ₅₃ O ₁₂ P
MK-13089C [298415]	i-Pr	C ₃₄ H ₅₃ O ₁₂ P

SOURCES – Meiji Seika; Mitsubishi Chemical.

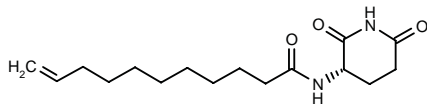
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1. Umagome, K. et al. (Meiji Seika Kaisha, Ltd.;Mitsubishi Chemical Corp.) *Novel triterpenes and their preparation method.* JP 2000319287.

NR58.4

300314

N-[2,6-Dioxopiperidin-3(S)-yl]-10-undecenamide



C16 H26 N2 O3; Mol wt: 294.3924

ACTION – Broad-spectrum chemokine inhibitor proven to inhibit leukocyte migration in response to MCP-1, MIP-1 α , IL-8 and SDF-1 α in the concentration range 1-10 nM, while having no effect on fMLP- or C5a-induced migration at up to 100 μ M. Compound appears to act by inhibiting chemokine signaling rather than as a chemokine receptor antagonist. *In vivo* studies showed strong inhibition of the upregulation of TNF- α induced by endotoxin in mice at 0.03 mg/kg s.c. Potentially useful as an antiinflammatory drug.

SOURCE – NeoRx.

REFERENCES

1. Grainger, D.J. and Tatalick, L.M. (NeoRx Corp.) *Cpds. and methods to inhibit or augment an inflammatory response*. WO 0042071.

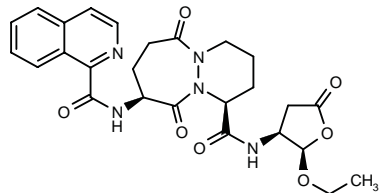
2. Grainger, D. et al. *Design, synthesis and initial characterisation of novel N-alkyl-3-aminoglutarimides as broad spectrum chemokine inhibitors related to peptide 3*. Chemokines Chemokine Receptors (Feb 16-21, Taos) 2001, Abst 316.

PRALNACASAN

252678

N-[2(R)-Ethoxy-5-oxotetrahydrofuran-3(S)-yl]-9(S)-(1-isoquinolinylcarboxamido)-6,10-dioxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1(S)-carboxamide

HMR-3480
VX-740



C26 H29 N5 O7; Mol wt: 523.5431

ACTION – Potent, orally available inhibitor of IL-1-converting enzyme (ICE, caspase 1), currently in phase II clinical trials for the treatment of rheumatoid arthritis.

SOURCES – Aventis Pharma; Vertex.

REFERENCES

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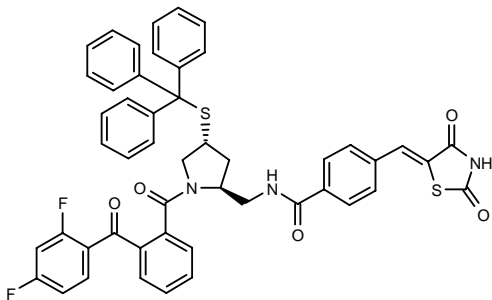
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PYRROPHENONE

300482

N-[1-[2-(2,4-Difluorobenzoyl)benzoyl]-4(R)-(triphenylmethylsulfanyl)pyrrolidin-2(S)-ylmethyl]-4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)benzamide



C49 H37 F2 N3 O5 S2; Mol wt: 849.9753

ACTION – An inhibitor of human cytosolic phospholipase A_{2 α} (cPLA_{2 α} ; IC₅₀ = 4.2 nM) proven to strongly inhibit A23187-induced arachidonic acid release from THP-1 cells and human whole blood (IC₅₀ = 24 and 190 nM, respectively). Compound was also found to inhibit A23187-induced PGE₂, TxB₂ and LTB₄ release from whole blood (IC₅₀ = 0.2, 0.15 and 0.32 μ M, respectively) and the magnitude of PGE₂ and TxB₂ inhibition was comparable to that of indomethacin. Potentially useful as an antiinflammatory agent.

SOURCE – Shionogi.

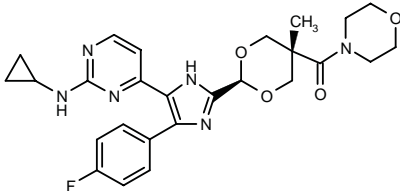
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RPR-203494

301441

trans-*N*-Cyclopropyl-4-[4-(4-fluorophenyl)-2-[5-methyl-5-(4-morpholinylcarbonyl)-1,3-dioxan-2-yl]-1 *H*-imidazol-5-yl]pyrimidin-2-amine



C26 H29 F N6 O4; Mol wt: 508.5511

ACTION – Inhibitor of p38 mitogen-activated protein (MAP) kinase (IC₅₀ = 9 nM), a pyrimidine analogue that is able to inhibit lipopolysaccharide (LPS)-induced TNF-α release in human monocytes (EC₅₀ = 60 nM). Compound exhibited good metabolic stability in rat hepatic microsomes and did not inhibit human cytochrome P-450 enzymes including CYP2D6, CYP1A2 and CYP2C9 at up to 50 μM. Pharmacokinetic studies in rats showed good oral bioavailability (48%) but a terminal elimination t_{1/2} after both i.v. and oral administration of only 1 h. In a model of rat streptococcal cell wall (SCW)-induced arthritis, doses of 10 and 30 mg/kg/day p.o. b.i.d. significantly inhibited ankle swelling. Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Aventis Pharma.

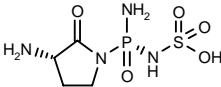
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IMMUNOMODULATING AGENTS

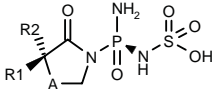
298096

(*R_p*)-Amino[3(*S*)-amino-2-oxopyrrolidin-1-yl]phosphorylsulfamic acid

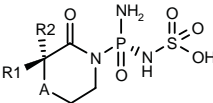


C4 H11 N4 O5 P S; Mol wt: 258.1939

ACTION – Potent inhibitor of dipeptidyl peptidase IV (IC₅₀ = 0.0039 μg/ml) with potential as an immuno-modulating, antiinflammatory and antiallergic agent in the treatment of HIV infection, as well as a hormone modulator. Other exemplified compounds from this series of sulphostin analogues include the following:



Compound	R1	R2	A	Formula
298097	H	NH2	-(CH2)2-	C ₅ H ₁₃ N ₄ O ₅ PS
298100	NH2	H	-(CH2)2-	C ₅ H ₁₃ N ₄ O ₅ PS
298102	H	NH2	-(CH2)3-	C ₆ H ₁₅ N ₄ O ₅ PS
298103	H	NH2	-CH2-	C ₄ H ₁₁ N ₄ O ₅ PS



Compound	R1	R2	A	Formula
298098	H	NH2	-CH2-	C ₅ H ₁₃ N ₄ O ₅ PS
298099	NH2	H	-CH2-	C ₅ H ₁₃ N ₄ O ₅ PS
298101	H	NH2	-(CH2)2-	C ₆ H ₁₅ N ₄ O ₅ PS

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

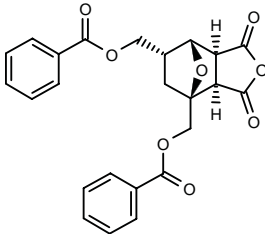
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298420

Benzoic acid (1*R**,2*S**,6*R**,7*S**,8*S**)-1-(benzoyloxy-methyl)-3,5-dioxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-8-ylmethyl ester

Benzoic acid (3*aR**,4*S**,6*R**,7*R**,7*aS**)-6-(benzoyloxy-methyl)-1,3-dioxohexahydro-4,7-epoxy-2-benzofuran-4(1*H*)-ylmethyl ester



C24 H20 O8; Mol wt: 436.4140

ACTION – Immunosuppressant, a selective inhibitor of protein phosphatase 2B (PP2B; IC₅₀ = 50 μM) that is completely devoid of inhibitory activity against PP1 and PP2A at 1 mM. Other exemplified compounds from this series of substituted 7-oxabicyclo[2.2.1]heptan-2,3-dicarboxylate derivatives are:

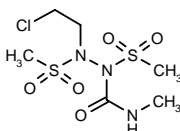
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

VNP-40101M*

247706

1-(2-Chloroethyl)-4-methyl-1,2-bis(methylsulfonyl)-semicarbazide



C6 H14 Cl N3 O5 S2; Mol wt: 307.7770

ACTION – Antineoplastic agent, an alkylating agent with an enhanced spectrum and improved antitumor activity compared to established alkylating agents against a variety of transplanted murine and human solid tumors including murine melanoma B16F10, lung carcinoma M109, reticulum cell sarcoma M5076 and human lung carcinoma LX-1. It also inhibits the DNA repair enzyme O-6-alkylguanine-DNA-alkyltransferase (AGT). In addition, compound shows excellent blood–brain barrier penetration in mice and high activity against intracranially implanted leukemia. Pharmacokinetic studies in rats following an i.v. dose of [¹⁴C]-labeled compound equivalent to 10 mg free base/kg showed rapid plasma elimination with a half-life of 15 min; most of the radioactivity was excreted in the urine as VNP-40101M and/or metabolites over the first 2 days and low levels of radioactivity were detected only in the blood, heart, lungs and spleen on day 7. Significant treatment-related toxicity was observed in dogs at doses > 10 mg/kg (as a single dose) or > 3 mg/kg/day for 5 days and included an increase in hepatic enzymes, decrease in red and white blood cell counts, hemorrhagic foci in the heart, kidney, lungs and enteric tissues, and death. Rats showed significant treatment-related toxicity at single or repeated doses of > 10 mg/kg. Selected for clinical evaluation.

SOURCES – Vion; Yale University, New Haven, CT (US).

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3. Finch, R.A. et al. *1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylamino)carbonylhydrazine (101M), a novel sulfonyl hydrazine prodrug with broad-spectrum antineoplastic activity*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4886.
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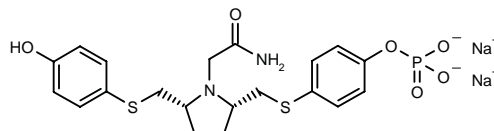
*Identified compound **247706** Drug Data Rep 1997, 019(05): 0455.

ANTIMETABOLITES

298920

Phosphoric acid 4-[1-(carbamoylmethyl)-5(*R*)-(4-hydroxyphenyl-sulfanylmethyl)-2(*S*) pyrrolidinylmethylsulfanyl]-phenyl ester disodium salt

2-[2(*R*)-(4-Hydroxyphenylsulfanylmethyl)-5(*S*)-[4-(phosphonooxy)phenylsulfanylmethyl]pyrrolidin-1-yl]-acetamide disodium salt



C20 H23 N2 Na2 O6 P S2; Mol wt: 528.4957

ACTION – Antineoplastic agent, a water-soluble, low-molecular-weight ribonucleotide reductase inhibitor (IC₅₀ = 6.28 μM against human enzyme) shown to inhibit the growth of HeLa S3 cells (IC₅₀ = 9.37 μM). A representative compound from a series of aryl phosphates.

SOURCES – Fuji Photo Film; Kyowa Hakko.

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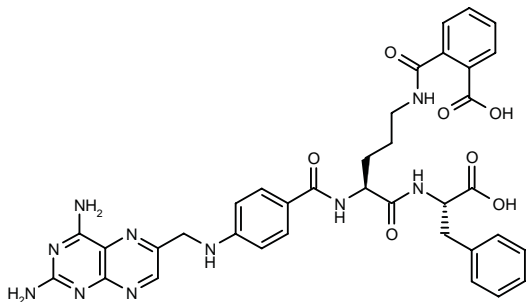
1. Kawakami, M. et al. (Kyowa Hakko Kogyo Co., Ltd.;Fuji Photo Film Co., Ltd.) *Aryl phosphates*. WO 0077014.

PT-633

301658

N^α-(4-Amino-4-deoxypteroyl)-*N*^δ-hemiphthaloyl-L-ornithyl-L-phenylalanine

N^δ-(2-Carboxybenzoyl)-*N*^α-[4-(2,4-diaminopteridin-6-ylmethylamino)benzoyl]-L-ornithyl-L-phenylalanine



C36 H36 N10 O7; Mol wt: 720.7434

ACTION – Prodrug for use in antibody-directed enzyme prodrug therapy (ADEPT) that is converted to L-phenylalanine and the cytotoxic antifolate PT-523* in the presence of carboxypeptidase A. Compound was found to strongly inhibit recombinant human dihydrofolate reductase in the presence of carboxypeptidase A ($K_i = 0.35 \text{ pM}$), whereas alone it showed little activity ($K_i > 10 \text{ }\mu\text{M}$). Moreover, in the presence of carboxypeptidase A it inhibited CEM cell growth ($\text{IC}_{50} = 0.2 \text{ nM}$), whereas it was much less active when given alone.

SOURCE – Dana-Farber Cancer Institute, Boston, MA (US).

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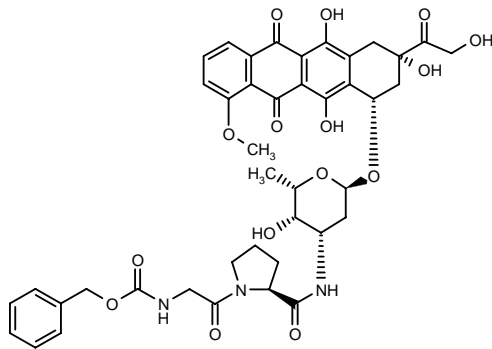
1. Wright, J.E. and Rosowsky, A. *Synthesis and biological testing of *N*^α-(4-amino-4-deoxypteroyl)-*N*^δ-hemiphthaloyl-L-ornithinyl-L-phenylalanine (PT633), a prodrug activated by carboxypeptidase A.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1584.

*See **N^δ-Hemiphthaloyl-APA-Orn** Drug Data Rep 1988, 010(09): 0764.

ANTIBIOTICS AND ALKALOIDS

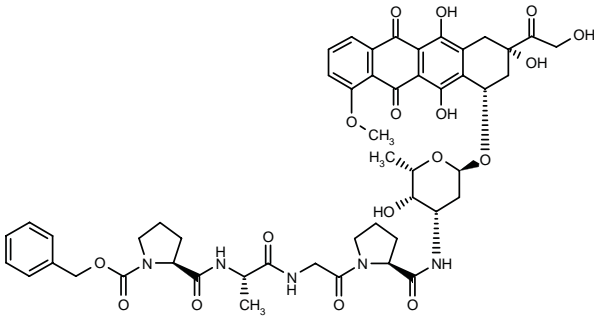
298162

N-(*N*-Benzyloxycarbonylglycyl-L-prolyl)doxorubicin



C42 H45 N3 O15; Mol wt: 831.8235

ACTION – Prodrug of the antitumor compound doxorubicin that is converted to the active drug at the site of the tumor by the action of endogenous fibroblast activation protein FAP- α , a protein shown to reside in human cancer tissues. This compound is particularly useful for the treatment of tumors which are associated with stromal fibroblasts that express FAP- α such as lung, breast and colon carcinomas, as well as bone and soft tissue sarcomas which express FAP- α . Another FAP-activated doxorubicin prodrug is:



298167: C50 H57 N5 O17

SOURCE – Boehringer Ingelheim.

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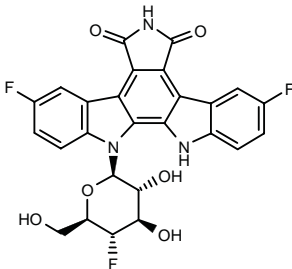
1. Park, J.E. et al. (Boehringer Ingelheim Pharma KG) *FAP-activated anti-tumor cpds.* WO 0071571.

DNA-INTERCALATING DRUGS

BMS-250749

301637

3,9-Difluoro-12-(4-deoxy-4-fluoro- β -D-glucopyranosyl)-5,6,12,13-tetrahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione



C26 H18 F3 N3 O6; Mol wt: 525.4372

ACTION – Antineoplastic agent, a potent inhibitor of topoisomerase I, proven to stabilize the covalent complexes formed between the enzyme and DNA, leading to single-strand DNA breaks and cell death by apoptosis. Compound, like camptothecin, induced apoptosis in human ovarian carcinoma A2780 cells containing wild-type or mutant *p53* and induced cell cycle arrest similar to that obtained with camptothecin. Compound displays broad-spectrum cytotoxic activity against human and murine cancer cells, with IC₅₀ values ranging from < 0.003 to 0.67 μM. It showed superior *in vivo* efficacy over currently marketed topo I inhibitors in animal models including lung, colon, ovarian and prostate carcinomas.

SOURCE – Bristol-Myers Squibb.

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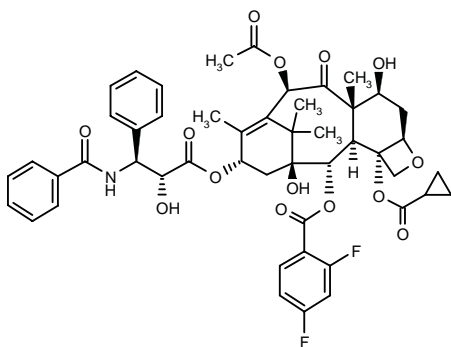
ANTIMITOTIC DRUGS

BMS-200532

299663

3(*S*)-Benzamido-2(*R*)-hydroxybenzenepropionic acid (2*aR*,4*S*,4*aS*,6*R*,9*S*,11*S*,12*S*,12*aR*,12*bS*)-6-acetoxy-12b-(cyclopropylcarbonyloxy)-12-(2,4-difluorobenzoyloxy)-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-5-oxo-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester

MC-134-248



C49 H51 F2 N O14; Mol wt: 915.9309

ACTION – Paclitaxel analogue with improved tubulin assembly activity compared to parent drug (EC₅₀ = 1.3 and 6.9 μM, respectively) and cytotoxicity against paclitaxel-resistant human colon carcinoma HCT 116/VM46 cells (IC₅₀ = 8.2 and 203 nM, respectively); the cytotoxicity against parental HCT 116 cells was comparable to that of paclitaxel (IC₅₀ = 2.1 and 2.0 nM, respectively).

SOURCES – Bristol-Myers Squibb; Virginia Polytechnic Institute and State University, Blacksburg, VA (US).

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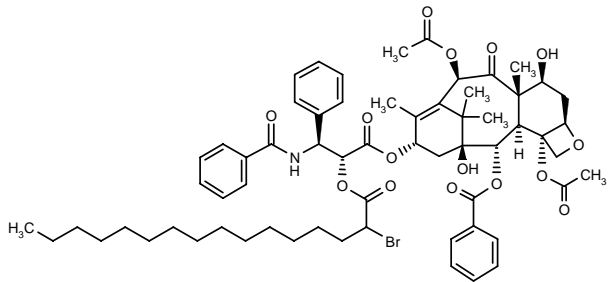
(–)-BRT-216

301519

(–)-3(*S*)-Benzamido-2(*R*)-(2-bromohexadecanoyloxy)-benzenepropionic acid (2*aR*,4*S*,4*aS*,6*R*,9*S*,11*S*,12*S*,12*aR*,12*bS*)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-5-oxo-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benzo[1,2-*b*]oxet-9-yl ester

(–)-[2*aR*-[α*α*,4β,4*a*β,6β,9α(2*R*,3*S*),11β,12α,12*a*α,12*b*α]]-6,12*b*-Diacetoxy-9-[3-benzamido-2-(2-bromohexadecanoyloxy)-3-phenylpropionyloxy]-12-(benzoyloxy)-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one

(–)-2-(2-Bromohexadecanoyl)paclitaxel



C63 H80 Br N O15; Mol wt: 1171.2210

ACTION – Antineoplastic agent, the (–)-enantiomer of the hydrophobic derivative of paclitaxel BRT-216, with improved activity and tolerability compared to both paclitaxel and the (+)-enantiomer. The maximum tolerated single i.v. dose of the compound was > 76 μmol/kg compared to 22.5-33.8 μmol/kg for paclitaxel. Compound was more effective than paclitaxel in delaying or inhibiting the growth of murine leukemia P388 and various human tumor xenografts including lung carcinoma A549, ovarian adenocarcinoma Caov-3, mammary carcinoma MX-1, pancreatic adenocarcinoma Capan-1, colon adenocarcinoma HT-29 and head and neck tumor SR475. In particular, compound was found to induce complete tumor regression in Caov-3, Capan-1, SR475 and MX-1 xenografts.

SOURCE – The Liposome Company (Elan).

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3. Ahmad, I. et al. *Growth inhibition of a human ovarian tumor by a novel paclitaxel derivative in SCID mice*. *Oncol Res* 1999, 11(6): 273.

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5. Ali, S. et al. *Hydrolyzable hydrophobic taxanes: Synthesis and anti-cancer activities*. *Anti-Cancer Drugs* 2001, 12(2): 117.

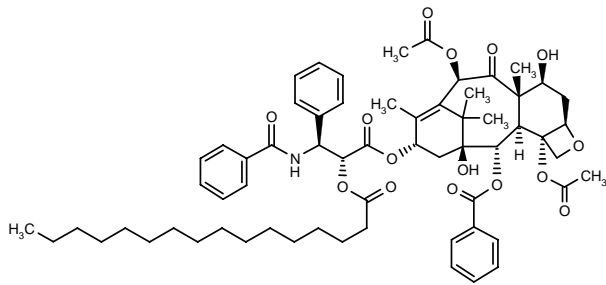
6. Masters, G.R. et al. *2'[(–)-2-Bromo-hexadecanoyl]paclitaxel ((–) Brt216) is more effective than Taxol® against seven established human tumor xenografts*. *Proc Amer Assoc Cancer Res* 2001, 42: Abst 460.

2'-PALMITOYLPACLITAXEL

301518

3(S)-Benzamido-2(R)-(hexadecanoyloxy)benzenepro-
pionic acid (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-
6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-
4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,
12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca-
[3,4]benz-[1,2-b]oxet-9-yl ester

[2aR-[2aα,4β,4aβ,6β,9α(2R,3S),11β,12α,12aα,12bα]]-
6,12b-Diacetoxy-9-[3-benzamido-2-(hexadecanoyloxy)-3-
phenylpropionyloxy]-12-(benzoyloxy)-4,11-dihydroxy-
4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-
dodecahydro-1H-7,11-methanocyclodeca[3,4]benz-
[1,2-b]oxet- 5-one



C63 H81 N O15; Mol wt: 1092.3250

ACTION – Paclitaxel derivative with improved anticancer activity and reduced toxicity compared to parent compound. The maximum tolerated i.v. dose of this compound formulated in Cremophor ELP:EtOH was 76 μmol/kg, which was more than 2-fold higher than that of paclitaxel. At equivalent i.v. doses of 15 μmol/kg, compound was at least as effective as paclitaxel in delaying tumor growth in 3 of 5 human tumor xenograft models in SCID mice (pancreatic Capan-1, ovarian Caov-3, lung A549, colon HT-29 and mammary MX-1). At the optimum dose of 60 μmol/kg, however, it induced a much greater delay in tumor growth compared to paclitaxel, producing complete and prolonged regression of Capan-1, Caov-3 and MX-1 solid tumors up to 150 days postimplantation.

SOURCE – The Liposome Company (Elan).

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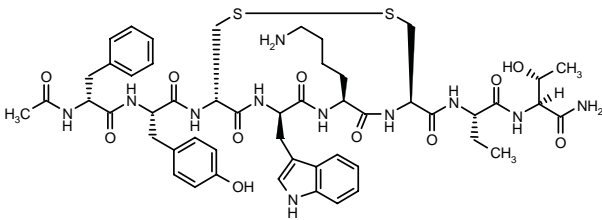
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HORMONAL AGENTS

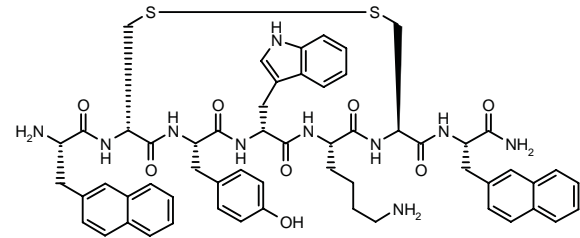
298604

N-Acetyl-D-phenylalanyl-L-tyrosyl-D-cysteinyl-D-tryptophyl-
L-lysyl-L-cysteinyl-2(S)-aminobutyryl-L-threoninamide
cyclic (3-6)-disulfide

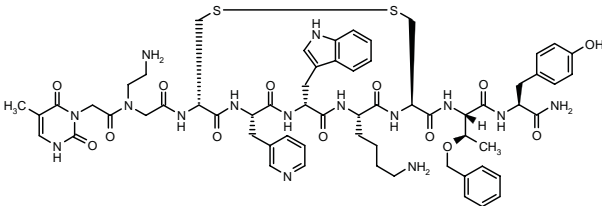


C51 H67 N11 O11 S2; Mol wt: 1074.2880

ACTION – Selective modulator of somatostatin and/or neuromedin B receptors, acting as an agonist. Potentially useful for treating a wide range of diseases including lung and other types of cancer, irritable bowel syndrome, pancreatitis, gastroesophageal reflux, diabetic neuropathy, etc. Other specifically claimed compounds include the following:



298605: C58 H64 N10 O8 S2



298619: C62 H77 N15 O13 S2

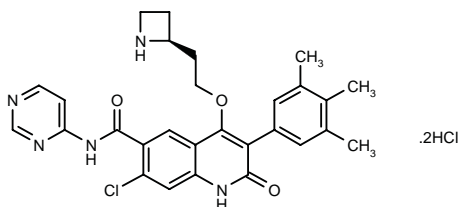
SOURCE – Biomeasure.

REFERENCES

1. Sadat-Aalaee, D. and Morgan, B.A. (Biomeasure Inc.) *Neuromedin B and somatostatin receptor agonists*. WO 0075186.

300646

4-[2-[2(*S*)-Azetidiny]ethoxy]-7-chloro-2-oxo-*N*-(4-pyrimidinyl)-3-(3,4,5-trimethylphenyl)-1,2-dihydroquinoline-6-carboxamide dihydrochloride



C₂₈ H₂₈ Cl N₅ O₃ · 2HCl; Mol wt: 590.9360

ACTION – Potent, nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist with subnanomolar binding affinity for human and monkey GnRH receptors (IC₅₀ = 0.44 and 0.5 nM, respectively). Compound exhibited excellent functional antagonism at the human GnRH receptor (IC₅₀ = 1 nM for inhibition of GnRH-stimulated phosphatidylinositol hydrolysis in CHO cells stably expressing human GnRH receptors). Intravenous administration of compound at 3 mg/kg to rhesus monkeys induced a long-lasting and significant decrease in serum levels (AUC) of luteinizing hormone (LH; 79%) and testosterone (T; 92%) compared with controls. Potentially useful for the treatment of sex hormone-related diseases including prostate cancer, breast cancer and endometriosis.

SOURCE – Merck & Co.

REFERENCES

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- DeVita, R.J. et al. *A potent, nonpeptidyl 1H-quinolone antagonist for the gonadotropin-releasing hormone receptor*. J Med Chem 2001, 44(6): 917.

LEUPROLIDE ACETATE IMPLANT**255455**

Drug-filled, miniature titanium implant for once-yearly dosing of leuprolide acetate

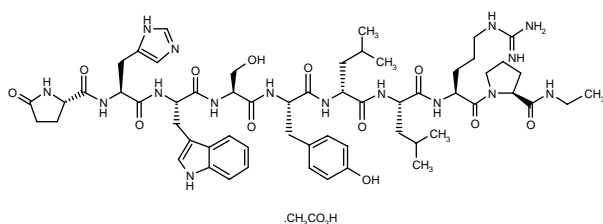
DUROS™-leuprolide

Leuprolide acetate

115073

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide mono-acetate salt

Leuprorelin acetate



C₅₉ H₈₄ N₁₆ O₁₂ · C₂ H₄ O₂; Mol wt: 1269.4640

ACTION – Luteinizing hormone-releasing hormone (LHRH) agonist that inhibits testosterone secretion when given continuously at therapeutic doses.

INDICATION – Palliative treatment of advanced prostate cancer.

PRESENTATION – Subcutaneous implant containing 72 mg leuprolide acetate (65 mg leuprolide free base) delivering 120 µg of leuprolide acetate per day over 12 months.

PROPRIETARY NAME – Viadur (US).

SOURCES – Alza; Bayer.

REFERENCES

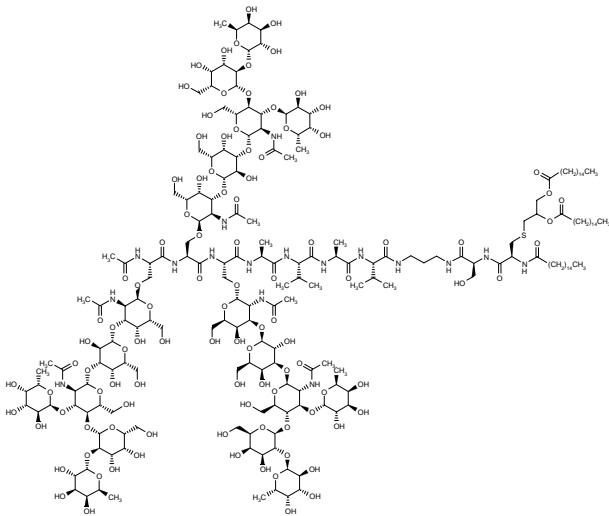
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- Fowler, J.E. et al. *A phase I/II dose ranging study of Duros™ (leuprolide) implantable therapeutic system in patients with advanced prostate cancer*. J Urol 1998, 159(5, Suppl.): Abst 1289.
- Fowler, J.E. et al. *Use of the Duros® leuprolide implant in patients with prostate cancer: Efficacy and safety results from two long-term phase I/II and III studies*. J Urol 2000, 163(4, Suppl.): Abst 1166.
- Fowler, J.E. Jr. et al. *Safety and efficacy of an implantable leuprolide delivery system in patients with advanced prostate cancer*. J Urol 2000, 164(3, Part 1): 730
- Fowler, J.E. et al. *Evaluation of an implant that delivers leuprolide for 1 year for the palliative treatment of prostate cancer*. Urology 2000, 55(5): 639.
- Johnson, P. et al. *A one-year implantable, osmotic delivery system (DUROS leuprolide implant) for the treatment of advanced prostate cancer*. Proc Control Release Soc 1997, 24: 59.
- Alza submits NDA for Viadur prostate cancer treatment. DailyDrugNews.com (Daily Essentials) 1999, May 28.
- Commercial rights to Viadur licensed to Bayer for advanced prostate cancer. DailyDrugNews.com (Daily Essentials) 2000, April 6.
- Duros leuprolide enters phase III for prostate cancer. DailyDrugNews.com (Daily Essentials) 1997, Oct 10.
- Launch announced for Viadur for advanced prostate cancer. DailyDrugNews.com (Daily Essentials) 2001, April 5.
- The FDA approves Viadur for once-yearly palliative treatment of advanced prostate cancer. DailyDrugNews.com (Daily Essentials) 2000, March 10.

CANCER IMMUNOTHERAPY

(Le^y)₃-Peptide-Pam₃Cys

301052

N-Acetyl-*O*-(6-deoxy- α -L-galactopyranosyl)-(1 \rightarrow 3)-(β -D-galactopyranosyl)-(1 \rightarrow 4)-[2-acetamido-2-deoxy-3-*O*-(6-deoxy- α -L-galactopyranosyl)- β -D-glucopyranosyl]-(1 \rightarrow 3)-(β -D-galactopyranosyl)-(1 \rightarrow 3)-(2-acetamido-2-deoxy- α -D-galactopyranosyl)-L-seryl-*O*-(6-deoxy- α -L-galactopyranosyl)-(1 \rightarrow 3)-(β -D-galactopyranosyl)-(1 \rightarrow 4)-[2-acetamido-2-deoxy-3-*O*-(6-deoxy- α -L-galactopyranosyl)- β -D-glucopyranosyl]-(1 \rightarrow 3)-(β -D-galactopyranosyl)-(1 \rightarrow 3)-(2-acetamido-2-deoxy- α -D-galactopyranosyl)-L-seryl-*O*-(6-deoxy- α -L-galactopyranosyl)-(1 \rightarrow 3)-(β -D-galactopyranosyl)-(1 \rightarrow 4)-[2-acetamido-2-deoxy-3-*O*-(6-deoxy- α -L-galactopyranosyl)- β -D-glucopyranosyl]-(1 \rightarrow 3)-(β -D-galactopyranosyl)-(1 \rightarrow 3)-(2-acetamido-2-deoxy- α -D-galactopyranosyl)-L-seryl-L-alanyl-L-valyl-L-alanyl-*N*¹-[3-[S-[2,3-bis(hexadecanoyloxy)propyl]-*N*-hexadecanoyl-D-cysteiny]-L-serylamino]propyl]-L-valinamide



C207 H359 N17 O103 S; Mol wt: 4766.1950

ACTION – Carbohydrate-based anticancer vaccine able to induce specific antitumor cell antibody responses, as demonstrated by measuring the reactivity of sera from immunized mice with ovarian cancer OVCAR-3 cells.

SOURCE – Memorial Sloan-Kettering Cancer Center, New York, NY (US).

REFERENCES

1. Danishefsky, S.J. et al. (Sloan-Kettering Institute for Cancer Research) *Trimeric antigenic O-linked glycopeptide conjugates, methods of preparation and uses thereof*. WO 9948515.

2. Glunz, P.W. et al. *Probing cell surface "glyco-architecture" through total synthesis. Immunological consequences of a human blood group determinant in a clustered mucin-like context*. J Am Chem Soc 1999, 121(45): 10636.

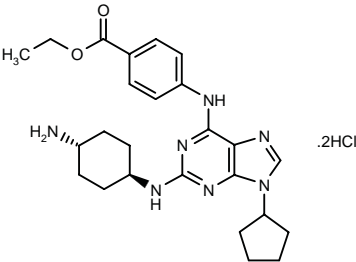
3. Glunz, P.W. et al. *Design and synthesis of Le^y-bearing glycopeptides that mimic cell surface Le^x mucin glycoprotein architecture*. J Am Chem Soc 2000, 122(30): 7273.

4. Kudryashov, V. et al. *Toward optimized carbohydrate-based anticancer vaccines: Epitope clustering, carrier structure, and adjuvant all influence antibody responses to Lewis^y conjugates in mice*. Proc Natl Acad Sci USA 2001, 98(6): 3264.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

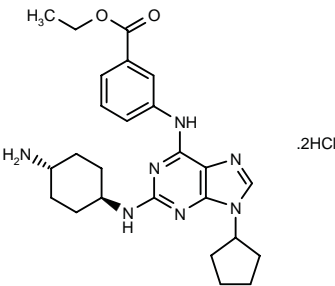
297925

trans-4-[2-(4-Aminocyclohexylamino)-9-cyclopentyl-9*H*-purin-6-ylamino]benzoic acid ethyl ester dihydrochloride



C25 H33 N7 O2 . 2HCl; Mol wt: 536.5045

ACTION – A selective inhibitor of cyclin-dependent kinases, particularly CDK1, CDK2, CDK4, CDK5 and CDK7, with antimitotic and antineurodegenerative properties. This compound is indicated for the treatment of tumors, psoriasis, neuronal apoptosis and Alzheimer's disease. Another exemplified purine derivative is:



297927: C25 H33 N7 O2 . 2HCl

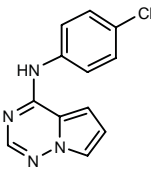
SOURCE – Aventis Pharma.

REFERENCES

1. Haesslein, J.-L. (Aventis SA) *Purine derivs., preparation method and pharmaceutical compsns. containing same*. WO 0071543.

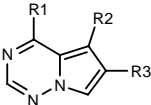
297996

N-(4-Chlorophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine



C12 H9 Cl N4; Mol wt: 244.6841

ACTION – Agent that inhibits tyrosine kinase activity of growth factor receptors such as VEGFR-2, FGFR-1, PDGFR, HER1 and HER2 and is thus useful for the treatment of conditions associated with angiogenesis and/or increased vascular permeability such as cancer. It is also expected to be useful for the treatment of inflammation, autoimmune diseases and disorders related to signal transduction pathways operating through growth factor receptors. Other specifically claimed pyrrolotriazine derivatives include the following:



Compound	R1	R2	R3	Formula
297997	2,3-dihydro-1-indolyl	Me	CO2Me	C ₁₇ H ₁₆ N ₄ O ₂
297998	1,4-dioxo-1,2,3,4-tetrahydro-6-phthalazinyl	Me	CO2Me	C ₁₇ H ₁₃ N ₅ O ₄
297999	2-oxo-2,3-dihydro-1H-indol-3-yl	Me	CO2H	C ₁₆ H ₁₂ N ₄ O ₃
298001	5-(MeNHSO ₂)-2-oxo-2,3-dihydro-1H-indol-3-yl	Me	CO2Me	C ₁₈ H ₁₇ N ₅ O ₅ S
298002	1-(PhCH ₂)-5-indazolyl-NH	Et	4-morpholinyl-CH ₂ CH ₂ OCH ₂	C ₂₉ H ₃₃ N ₇ O ₂
298003	4-Br-PhNH	Et	CO ₂ Et	C ₁₇ H ₁₇ BrN ₄ O ₂
298005	3-OH-4-Me-PhNH	Me	2H-1,2,3-triazol-2-yl-(CH ₂) ₃ O	C ₁₉ H ₂₁ N ₇ O ₂
298006	1-(PhCH ₂)-5-indazolyl-NH	H	CO ₂ Me	C ₂₂ H ₁₈ N ₆ O ₂

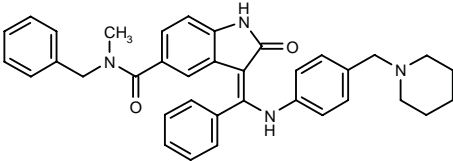
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Hunt, J.T. et al. (Bristol-Myers Squibb Co.) *Pyrrolotriazine inhibitors of kinases*. WO 0071129.

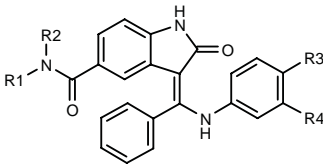
298246

(Z)-N-Benzyl-N-methyl-2-oxo-3-[1-phenyl-1-[4-(1-piperidinylmethyl)phenylamino]methylene]-2,3-dihydro-1H-indole-5-carboxamide



C36 H36 N4 O2; Mol wt: 556.7064

ACTION – Antineoplastic agent with inhibitory activity against different kinases and cyclin/cyclin-dependent kinase (CDK) complexes. *In vitro*, compound displayed potent antiproliferative activity against leiomyosarcoma cancer SK-UT-1B cells, with an IC₅₀ value of 0.001 μM. Other specifically claimed compounds from this series of substituted indolinones are:



Compound	R1	R2	R3	R4	Formula
298249	Me	Ph	CH ₂ N(Me)CH ₂ Ph	H	C ₃₈ H ₃₄ N ₄ O ₂
298253	Me	CH ₂ Ph	H	CH ₂ N(Me) ₂	C ₃₃ H ₃₂ N ₄ O ₂
298256		-(CH ₂) ₅ -	1-Pip-CH ₂	H	C ₃₃ H ₃₆ N ₄ O ₂
298258	Me	Ph	CH ₂ N(Me) ₂	H	C ₃₂ H ₃₀ N ₄ O ₂
298261	Me	CH ₂ Ph	CH ₂ N(Me) ₂	H	C ₃₃ H ₃₂ N ₄ O ₂
298263	H	cyclohexyl-CH ₂	CH ₂ N(Me) ₂	H	C ₃₂ H ₃₆ N ₄ O ₂
298264	H	Bu	N(SO ₂ Me)-CH ₂ CH ₂ N(Me) ₂	H	C ₃₁ H ₃₇ N ₅ O ₄ S
298265	H	Bu	N(COEt)-CH ₂ CH ₂ N(Me) ₂	H	C ₃₃ H ₃₈ N ₅ O ₃
298266	H	3-Cl-PhCH ₂	CH ₂ N(Me) ₂	H	C ₃₂ H ₂₉ ClN ₄ O ₂
298267	H	Bu	CH ₂ N(Me) ₂	H	C ₂₉ H ₃₂ N ₄ O ₂

SOURCE – Boehringer Ingelheim.

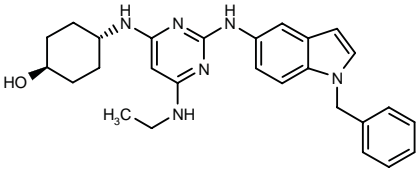
REFERENCES

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CINK4

290718

trans-4-[2-(1-Benzyl-1H-indol-5-ylamino)-6-(ethylamino)-pyrimidin-4-ylamino]cyclohexanol



C27 H32 N6 O; Mol wt: 456.5908

ACTION – Cyclin-dependent kinase 4 (CDK4)/cyclin D1 inhibitor (IC₅₀ = 1.5 μM) with high selectivity over other cyclin-dependent kinases including CDK1, CDK2, CDK5 and CDK6 (IC₅₀ > 50 μM), as well other tyrosine kinases such as v-abl, c-met, insulin-like growth factor (IGF-I) and insulin receptor kinases (IC₅₀ > 10 μM). Consistent with inhibition of CDK4, compound induced arrest in the G1 phase of the cell cycle of asynchronous human MRC-5 fibroblasts and human osteosarcoma U2OS cells, and prevented CDK4 from phosphorylating retinoblastoma protein pRb. In nude mice bearing human colon carcinoma HCT 116 xenografts, a dose of 30 mg/kg i.p. every 12 h produced a significant reduction in tumor volume. Potentially useful as a selective treatment for tumors lacking the tumor suppressor p16 or containing deregulated CDK4 activity including non-small cell lung cancer.

SOURCE – Novartis.

REFERENCES

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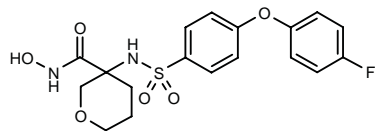
2. Soni, R. et al. *Novel 2,4,6-triaminopyrimidine selectively inhibits CDK4/cyclin D1 activity in cancer cells.* 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst A-22.

3. Soni, R. et al. *Selective in vivo and in vitro effects of a small molecule inhibitor of cyclin-dependent kinase 4.* J Natl Cancer Inst 2001, 93(6): 436.

ANGIOGENESIS INHIBITORS

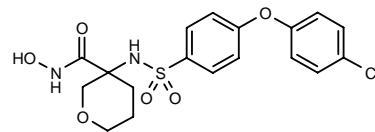
298338

3-[4-(4-Fluorophenoxy)phenylsulfonamido]tetrahydro-2H-pyran-3-carboxylic acid



C18 H19 F N2 O6 S; Mol wt: 410.4201

ACTION – Matrix metalloproteinase inhibitor, potentially useful for the treatment of inflammatory disorders and cancer. Another specifically claimed 3-(arylsulfonylamino)tetrahydropyran-3-carboxylic acid hydroxamide is:



298339: C18 H19 Cl N2 O6 S

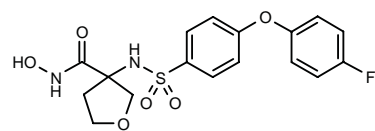
SOURCE – Pfizer.

REFERENCES

1. Reiter, L.A. (Pfizer Products Inc.) *3-(Arylsulfonylamino)-tetrahydropyran-3-carboxylic acid hydroxamides.* WO 0073295.

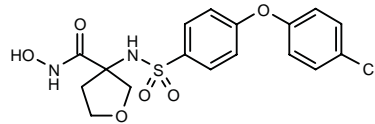
298355

3-[4-(4-Fluorophenoxy)phenylsulfonamido]tetrahydro-furan-3-carboxylic acid



C17 H17 F N2 O6 S; Mol wt: 396.3933

ACTION – Matrix metalloproteinase inhibitor, potentially useful for the treatment of inflammatory disorders and cancer. Another specifically claimed 3-(arylsulfonylamino)tetrahydrofuran-3-carboxylic acid hydroxamide is:



298356: C17 H17 Cl N2 O6 S

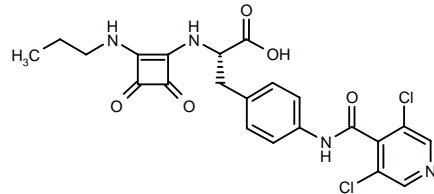
SOURCE – Pfizer.

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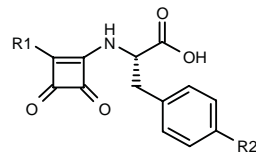
298357

4-(3,5-Dichloropyridin-4-ylcarboxamido)-N-[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]-L-phenylalanine



C22 H20 Cl2 N4 O5; Mol wt: 491.3290

ACTION – Inhibitor of the binding of integrins to their ligands that modulates cell adhesion and is expected to be useful for the treatment of tumors, retinopathy, macular degeneration, psoriasis, rheumatoid arthritis, osteoporosis, hypercalcemia, Paget's disease, hyperparathyroidism, inflammatory bowel disease and psoriasis, among others. Other specifically claimed squaric acid derivatives are:



Compound	R1	R2	Formula
298358	t-Bu	3,5-(Cl)2-4-Pyr-CONH	C ₂₃ H ₂₁ Cl ₂ N ₃ O ₅
298359	N(Et)2	6,7-(MeO)2-4-quinazolinyl-NH	C ₂₇ H ₂₉ N ₅ O ₆
298360	N(Et)2	2,6-naphthyridin-1-yl-NH	C ₂₈ H ₂₅ N ₅ O ₄
298361	N(Et)2	6,7-(MeO)2-4-quinazolinyl-O	C ₂₇ H ₂₈ N ₄ O ₇
298362	N(Pr)2	2,6-naphthyridin-1-yl-NH	C ₂₇ H ₂₉ N ₅ O ₄
298363	N(Et)2	2,6-naphthyridin-1-yl-O	C ₂₈ H ₂₄ N ₄ O ₅
298364	1-Pip	2,6-naphthyridin-1-yl-NH	C ₂₈ H ₂₅ N ₅ O ₄
298365	N(Et)2	3,5-(Cl)2-4-Pyr-CONH	C ₂₃ H ₂₂ Cl ₂ N ₄ O ₅
298366	N(Pr)2	2,6-naphthyridin-1-yl-O	C ₂₇ H ₂₈ N ₄ O ₅
298367	i-PrN(Et)	2,6-naphthyridin-1-yl-NH	C ₂₈ H ₂₇ N ₅ O ₄

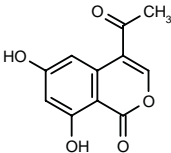
SOURCE – Celltech Group.

REFERENCES

1. Langham, B.J. et al. (Celltech Chiroscience Ltd.) *Squaric acid derivs. as cell adhesion molecules*. WO 0073260.

298603

4-Acetyl-6,8-dihydroxy-1*H*-2-benzopyran-1-one



C11 H8 O5; Mol wt: 220.1792

ACTION – Angiogenesis inhibitor isolated from the fungus *Sesquicillium* sp. Y70382 and expected to be useful for the treatment of cancer, rheumatoid arthritis and diabetic retinopathy. The compound exhibited inhibitory activity against human umbilical vein endothelial cell (HUVEC) differentiation into capillary tubes (50, 85 and 100% inhibition at 0.2, 0.5 and 1.0 µg/ml, respectively), whereas it did not show cytotoxicity to HUVEC at these concentrations. Its antiangiogenic activity was assessed in a chorioallantoic membrane assay in chick eggs, with 50.0 and 93.3% inhibition of angiogenesis at 1 and 10 µg/egg, respectively. When administered orally to rats, an LD₅₀ of at least 300 mg/kg was determined.

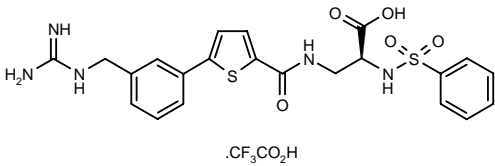
SOURCE – Korea Research Institute of Bioscience and Biotechnology, Taedok Science Town (KR).

REFERENCES

1. Lee, J.J. et al. (Korea Research Institute of Bioscience and Biotechnology) *Novel isocoumarin derivs. inhibiting angiogenesis*. WO 0075124.

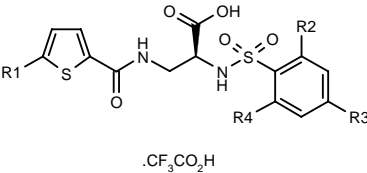
298800

3-[5-[3-(Guanidinomethyl)phenyl]thien-2-ylcarboxamido]-2(*S*)-(phenylsulfonamido)propionic acid trifluoroacetate



C22 H23 N5 O5 S2 . C2 H F3 O2; Mol wt: 615.6076

ACTION – Integrin, particularly α_vβ₃ and α_vβ₅, antagonist with potential for the treatment of cancer, osteoporosis, restenosis and ocular neovascularization. *In vitro*, compound gave IC₅₀ values for fibrinogen binding to immobilized α_vβ₃ and gpIIb/IIIa of 2.7 and 0.55 nM, respectively. When tested for cytotoxicity against HMVEC, HT-29 and B16F10 cell lines, compound gave IC₅₀ values of 0.20, > 10 and 1.3 µM, respectively. Other compounds from this series of thiophene derivatives include the following:



Compound	R1	R2=R3=R4	Formula
298801	3-[CH2NHC(=NH)NH2]-Ph	Me	C ₂₇ H ₃₀ F ₃ N ₅ O ₇ S ₂
298802	3-[NH2C(=NH)NH]-Ph	H	C ₂₃ H ₂₂ F ₃ N ₅ O ₇ S ₂
298803	3-[NH2C(=NH)NH]-Ph	Me	C ₂₆ H ₂₈ F ₃ N ₅ O ₇ S ₂
298804	CH=CHCH2NHC(=NH)NH2	Me	C ₂₃ H ₂₈ F ₃ N ₅ O ₇ S ₂

SOURCE – BioChem Pharma.

REFERENCES

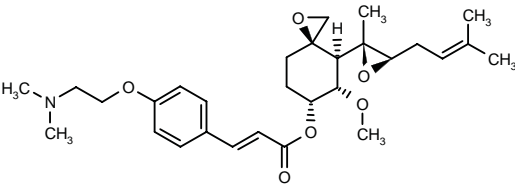
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CKD-732*

283541

3-[4-[2-(Dimethylamino)ethoxy]phenyl]-2(*E*)-propenoic acid (3*R*,4*S*,5*S*,6*R*)-4-[2(*R*)-methyl-3(*R*)-(3-methyl-2-butenyl)oxiran-2-yl]-5-methoxy-1-oxaspiro[2.5]oct-6-yl ester

6-*O*-[3-[4-[2-(Dimethylamino)ethoxy]phenyl]-2(*E*)-propenoyl]fumagillol



C29 H41 N O6; Mol wt: 499.6439

ACTION – Antiangiogenic agent, a fumagillin derivative shown to inhibit the proliferation and migration of endothelial cells and to exert antitumor and antimetastatic activity in animal models. When given in combination with doxorubicin, 5-fluorouracil or cisplatin, it showed synergistic effects on tumor growth in mice bearing melanoma B16BL6 or Lewis lung carcinoma. In preliminary toxicity studies in mice, compound given at doses of 150-230 mg/kg i.p. was less toxic than TNP-470, another fumagillin analogue currently undergoing clinical trials, as regards lethality and hematopoietic toxicity.

SOURCE – Chong Kun Dang.

REFERENCES

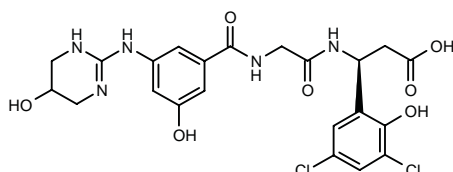
1. Hong, C.I. et al. (Chong Kun Dang Corp.) *Fumagillol derivs. and processes for preparing the same*. US 6063812, WO 9959986.
2. Park, H.-J. et al. *Combination chemotherapy and preliminary toxicity of CKD-732, a novel fumagillin derivative*. Proc Amer Assoc Cancer Res 2001, 42: Abst 471.

*Identified compound **283541** (see **283522**) Drug Data Rep 2000, 022(03): 0284.

S-787***280966**

3(S)-(3,5-Dichloro-2-hydroxyphenyl)-3-[2-[3-hydroxy-5-(5-hydroxy-1,4,5,6-tetrahydropyrimidin-2-ylamino)benz-amido]acetamido]propionic acid

N-[3-Hydroxy-5-(5-hydroxy-1,4,5,6-tetrahydropyrimidin-2-ylamino)benzoyl]glycyl-3(S)-(3,5-dichloro-2-hydroxyphenyl)-β-alanine



C22 H23 Cl2 N5 O7; Mol wt: 540.3577

ACTION – Orally active integrin $\alpha_v\beta_3$ (vitronectin) receptor antagonist ($IC_{50} = 0.7$ nM for binding inhibition in a solid-phase $\alpha_v\beta_3$ receptor assay) shown to induce apoptosis of human glioblastoma SNB-19 cells (IC_{50} approx. 2 μ M) and to significantly inhibit the angiogenesis and growth of human glioma U-87 cells implanted in athymic rats at 30 mg/kg p.o., b.i.d. for 3 weeks. In addition, it dose-dependently (0.4-40 mg/kg p.o.) prevented loss of trabecular bone marrow density in a model of estrogen deficiency-induced bone wasting in ovariectomized rats.

SOURCE – Pharmacia.

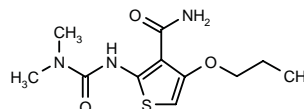
REFERENCES

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- Rogers, T.E. and Ruminski, P.G. (Pharmacia Corp.) *Meta-azacyclic amino benzoic acid cpds. and derivs. thereof being integrin antagonists*. EP 1060164, WO 9944994.
- Ruminski, P.G. et al. (Pharmacia Corp.) *Meta-guanidine, urea, thiourea or azacyclic amino benzoic acid derivs. as integrin antagonists*. EP 0850221, JP 1999510814, US 6013651, US 6100423, WO 9708145.
- Roberts, T.P. et al. *A magnetic resonance imaging study of the efficacy of S-787, an orally active $\alpha_v\beta_3$ antagonist in a rat model of human glioblastoma*. Proc Amer Assoc Cancer Res 2001, 42: Abst 583.
- Rogers, T.E. et al. *Potent, selective and orally active antagonists of integrin $\alpha_v\beta_3$ angiogenesis inhibitors. The discovery of the S 787 class of integrin antagonists*. Proc Amer Assoc Cancer Res 2001, (Suppl.): Abst LB-4.
- Rogers, T.E. et al. *Potent, selective, and orally active antagonists of integrin $\alpha_v\beta_3$ as tumor angiogenesis inhibitors: The discovery of the S 257-class of integrin antagonist*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 225.
- Settle, S.L. et al. *An oral peptidomimetic antagonist of integrin $\alpha_v\beta_3$ inhibits ovariectomy-induced bone loss in the rat*. J Bone Miner Res 1999, 14(Suppl. 1): Abst SU410.
- Uhm, J.H. et al. *S-787, a peptidomimetic inhibitor of the vitronectin receptor ($\alpha_v\beta_3$ integrin), induces apoptosis in glioma cells with a reduction in the level of focal adhesion kinase*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1636.

*Identified compound **280966** (see **280962**) Drug Data Rep 1999, 021(11): 1032.

OTHER ONCOLYTIC DRUGS**297923**

2-(3,3-Dimethylureido)-4-propoxythiophene-3-carboxamide



C11 H17 N3 O3 S; Mol wt: 271.3393

ACTION – A representative heterocyclic compound useful for the treatment of cancer and other hyperproliferative disorders such as psoriasis and benign prostatic hyperplasia.

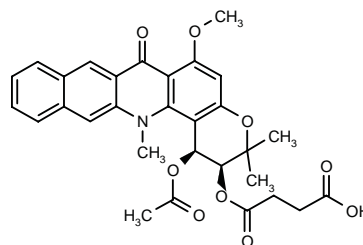
SOURCE – Pfizer.

REFERENCES

- Gant, T.G. and Noe, M.C. (Pfizer Products Inc.) *Heterocyclic derivs. useful as anticancer agents*. WO 0071532.

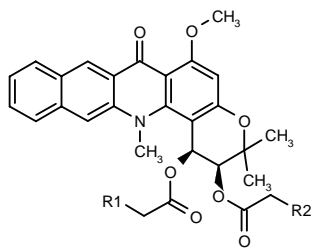
298280

(±)-cis-4-(1-Acetoxy-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yloxy)-4-oxobutyric acid



C30 H29 N O9; Mol wt: 547.5571

ACTION – Antineoplastic agent with good water solubility and cytotoxicity against murine leukemia L1210 and human colon carcinoma HT-29 cells ($IC_{50} = 2$ μ M). In addition, compound is reported to exhibit antitumor activity *in vivo* in mice bearing murine P388 leukemia or s.c.-implanted colon adenocarcinomas C38. Other specifically claimed compounds from this series of 7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridine carboxylate derivatives are:



Compound	R1	R2	Formula
298484	CH2CO2H	CH2CO2H	C ₃₂ H ₃₁ NO ₁₁
298486	H	CH2CH2CO2H	C ₃₁ H ₃₁ NO ₉
298487	H	N(Me)2	C ₃₀ H ₃₂ N ₂ O ₇
298488	H	CH2CH2N(Me)2	C ₃₂ H ₃₆ N ₂ O ₇

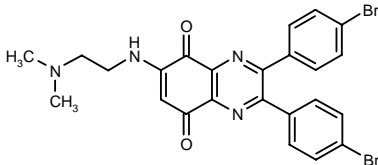
SOURCE – ADIR.

REFERENCES

1. Koch, M. et al. (ADIR et Cie.) 7-Oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]-acridine carboxylate derivs., process for their preparation and pharmaceutical compsns. containing them. EP 1061081, FR 2795071, JP 2001011078.

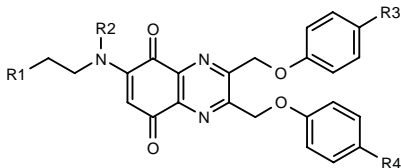
298282

2,3-Bis(4-bromophenyl)-6-[2-(dimethylamino)ethylamino]-5,8-dihydroquinoxaline-5,8-dione

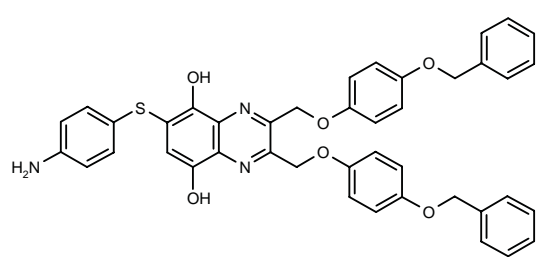


C24 H20 Br2 N4 O2; Mol wt: 556.2560

ACTION – Antineoplastic agent proven to inhibit the proliferation of human lung carcinoma A549 cells with an IC₅₀ value of 2.4 μM. Other exemplified compounds from this series of quinoxaline derivatives include the following:



Compound	R1	R2	R3=R4	Formula
298284	N(Me)2	H	CH2Ph	C ₄₀ H ₃₈ N ₄ O ₄
298285	N(Me)2	Me	CH2Ph	C ₄₁ H ₄₀ N ₄ O ₄
298286	CH2N(Me)2	H	CH2Ph	C ₄₁ H ₄₀ N ₄ O ₄
298287	4-morpholinyl	H	CH2Ph	C ₄₂ H ₄₀ N ₄ O ₅
298288	N(Me)2	H	OPh	C ₃₈ H ₃₄ N ₄ O ₆
298289	N(Me)2	H	OCH2Ph	C ₄₀ H ₃₈ N ₄ O ₆
298290	N(Me)2	H	2-Pyr-CH2CH2	C ₄₀ H ₄₀ N ₆ O ₄



298283: C42 H35 N3 O6 S

SOURCE – Kyowa Hakko.

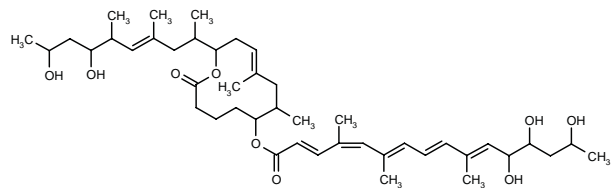
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MYCOLACTONE A

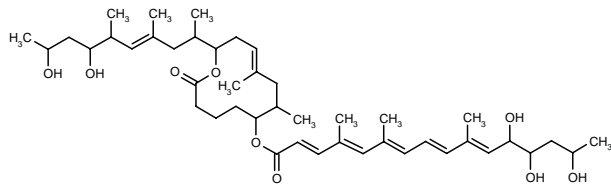
298799

12,13,15-Trihydroxy-4,6,10-trimethyl-2(E),4(Z),6(E),8(E),10(E)-hexadecapentaenoic acid 12-[6,8-dihydroxy-1,3,5-trimethyl-3(E)-nonenyl]-7,9-dimethyl-2-oxooxacyclododec-9-en-6-yl ester



C44 H70 O9; Mol wt: 743.0280

ACTION – Polyketide macrolide toxin isolated from virulent cultures of *Mycobacterium ulcerans*, the causative agent of buruli ulcers, with the ability to inhibit cancer and suppress inflammatory responses. Mycolactone was found to potently inhibit the growth of lung cancer H460, breast cancer MCF-7 and CNS cancer SF-268 cells, and to reduce the inflammatory reaction in guinea pigs inoculated with an infectious quantity of *Mycobacterium marinum*. A minor component isolated from the same culture is:



Mycolactone B [305776]: C44 H70 O9

SOURCE – US Department of Health & Human Services (US).

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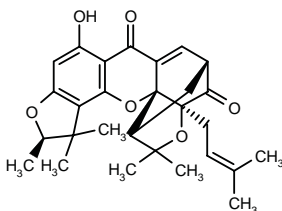
2. Gunawardana, G. et al. Characterization of novel macrolide toxins mycolactones A and B, from a human pathogen, *Mycobacterium ulcerans*. J Am Chem Soc 1999, 121(25): 6092.

SOOTEPENSEONE

298712

(1*S*,3*aR*,5*R*,11*R*,13*aR*)-8-Hydroxy-3,3,11,12,12-pentamethyl-1-(3-methyl-2-butenyl)-3*a*,4,5,7,11,12-hexahydro-1,5-methano-1*H*,3*H*-difuro[2,3-*c*:3',4'-*g*]-xanthene-7,14-dione

D-25637



C28 H32 O6; Mol wt: 464.5548

ACTION – Antineoplastic agent isolated from *Dasy-maschalon sootepense* Craib, Annonaceae, proven to exhibit cytotoxicity against epidermoid carcinoma KB, murine lymphatic leukemia L1210, prostate carcinoma LNCaP and human ovarian carcinoma SK-OV-3, giving IC₅₀ values of 1.74 µg/ml against the four cell lines, compared to IC₅₀ values of 0.17, 0.17 and 1.74 µg/ml, respectively, for actinomycin D, 0.17, 0.017, 0.17 and 0.17 µg/ml, respectively, for doxorubicin, 0.17, 0.017, 0.17 and 0.17 µg/ml, respectively, for bleomycin, and 0.17, 0.017, 0.17 and 0.17 µg/ml, respectively, for vinblastine. *In vivo*, compound was active in a hollow fiber assay, giving 49 and 41% inhibition of epidermoid carcinoma KB and human breast carcinoma MCF-7 tumor growth at 4 x 10 mg/kg i.p., exhibiting comparable or superior activity to the reference compounds. In addition, it was shown to be less toxic than the standard compounds, with an LD₅₀ value in mice of > 100 mg/kg i.p. vs. LD₅₀ values of ca. 1, ca. 6, ca. 40 and ca. 80 mg/kg i.p., respectively, for actinomycin D, vinblastine, doxorubicin and bleomycin.

SOURCE – Asta Medica.

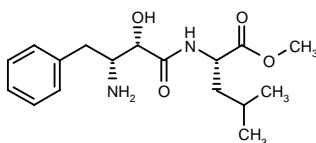
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UBENIMEX METHYL ESTER

298562

N-[3(*R*)-Amino-2(*S*)-hydroxy-4-phenylbutyryl]-L-leucine methyl ester



C17 H26 N2 O4; Mol wt: 322.4024

ACTION – A representative compound from a series of ubenimex derivatives with apoptosis-inducing activity. *In vitro*, compound inhibited the proliferation of U-937 cells with an IC₅₀ value of 15 ng/ml and was further shown to inhibit the degradation of Ala-MCA, Leu-MCA and Met-MCA by aminopeptidases with respective IC₅₀ values of 23, 81 and 68 ng/ml. In addition, it was shown to activate caspase 3 (CPP32) *in vitro* in U-937 cells at a concentration of 10 µg/ml.

SOURCE – Nippon Kayaku.

REFERENCES

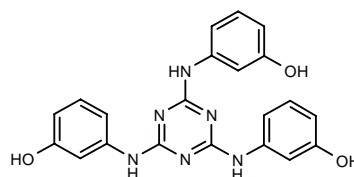
1. Sekine, K. et al. (Nippon Kayaku Co., Ltd.) *Apoptosis inducers*. JP 2000327568.

WHI-P233

299113

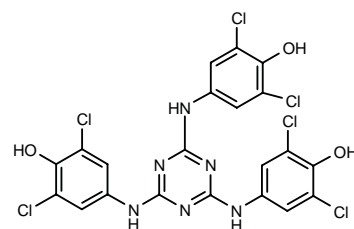
3-[4,6-Bis(3-hydroxyphenylamino)-1,3,5-triazin-2-yl-amino]phenol

2,4,6-Tris(3-hydroxyphenyl)-1,3,5-triazine



C21 H18 N6 O3; Mol wt: 402.4122

ACTION – Potent cytotoxic agent, particularly active against human breast cancer and leukemia cell lines. WHI-P233 was effective against leukemia NALM-6 cells (IC₅₀ = 5.1 µM), breast cancer BT-20 cells (IC₅₀ = 66.1 µM), prostate cancer PC-3 cells (IC₅₀ = 45.1 µM) and brain tumor U-373 cells (IC₅₀ = 104.4 µM). Another exemplified melamine derivative is:



WHI-P239 [299114]: C21 H12 Cl6 N6 O3

SOURCE – Parker Hughes Institute, Roseville, MN (US).

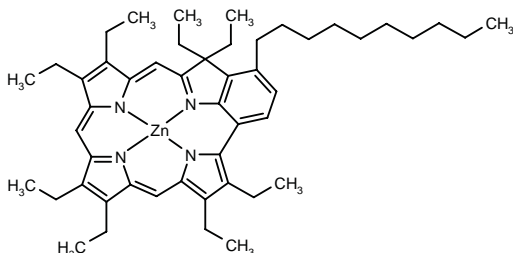
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PHOTOSENSITIZERS

301352

[2¹-Decyl-3,3,7,8,12,13,17,18-octaethyl-3*H*-benzo-[a]porphyrinato(2-)]zinc



C49 H66 N4 Zn; Mol wt: 776.4784

ACTION – Photosensitizing agent for photodynamic therapy, a highly lipophilic compound showing high and selective tumor uptake after a dose of 5 µmol/kg to mice bearing fibrosarcoma RIF-1 tumors. In Molt-4 cells, a concentration of 2.5 µM with a light dose of 4.0 J/cm², produced high photocytotoxicity without any dark toxicity. Further *in vivo* studies are currently in progress.

SOURCE – Roswell Park Cancer Institute, Buffalo, NY (US).

REFERENCES

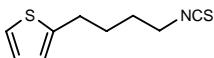
1. Li, G. et al. *A simple and efficient approach for the synthesis of fluorinated and nonfluorinated octaethylporphyrin-based benzochlorins with variable lipophilicity. Their in vivo tumor uptake, and the preliminary in vitro photosensitizing.* J Org Chem 2001, 66(4): 1316.

CHEMOPREVENTIVE AGENTS

298561

2-(4-Isothiocyanatobutyl)thiophene

4-(2-Thienyl)butyl isothiocyanate



C9 H11 N S2; Mol wt: 197.3249

ACTION – Agent for the treatment or prevention of cancer and precancerous conditions, a representative compound from a series of 5-membered heterocyclic compounds bearing an alkylisothiocyanate moiety that act by inducing phase II enzymes, particularly glutathione S-transferase (GST). Compound exhibited similar or greater potency in inducing GST activity compared to the known compounds phenylbutylisothiocyanate (PBITC) and 2-butylthiophene (2-BT) when administered orally to mice. In addition, it was found to inhibit DMH-induced colonic aberrant crypt formation when given at 0.5 mmol/day p.o., being more potent than 2-BT at the same dose.

SOURCE – LKT Laboratories.

REFERENCES

1. Lam, L.K.T. (LKT Laboratories, Inc.) *Heterocyclic cpds. for cancer chemoprevention.* US 6166003.

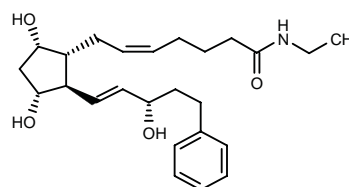
OCULAR MEDICATIONS

BIMATOPROST

251988

(5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-*N*-ethyl-5-heptenamide

AGN-192024



C25 H37 N O4; Mol wt: 415.5703

ACTION – Synthetic prostamide analogue with ocular hypotensive activity.

INDICATION – Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

PRESENTATION – Ophthalmic solution, 0.03%.

PROPRIETARY NAME – Lumigan (US).

SOURCE – Allergan.

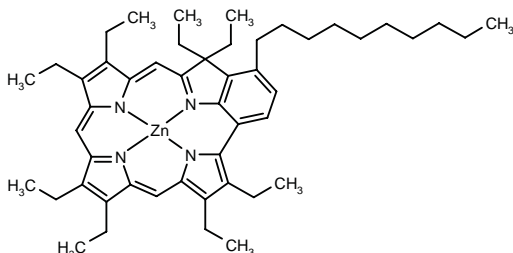
REFERENCES

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2. Woodward, D.F. et al. (Allergan, Inc.) *Non-acidic cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl derivs. as therapeutic agents.* EP 0660716, JP 1996501310, US 5352708, WO 9406433.
3. Woodward, D.F. et al. (Allergan, Inc.) *Non-acidic cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl derivs. as therapeutic agents.* US 5607978.
4. Woodward, D.L. et al. (Allergan, Inc.) *Non-acidic cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl derivs. as therapeutic agents.* US 5688819, WO 9730710.
5. Brandt, J.D. *Phase III, 3-month comparison of timolol with AGN-192024: A new ocular hypotensive lipid (HTL(TM)) for glaucoma management.* Annu Meet Am Acad Ophthalmol (Oct 22-25, Dallas) 2000, Abst PA022.
6. Brubaker, R.F. *Mechanism of action of AGN 192024, a new ocular hypotensive agent.* 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 22.
7. Brubaker, R.F. et al. *Effects of AGN 192024, a new ocular hypotensive agent, on aqueous dynamics.* Am J Ophthalmol 2001, 131(1): 19.
8. Cantor, L.B. et al. *6-Month comparison of AGN 192024 once-daily and twice-daily with timolol twice-daily in patients with elevated IOP.* Annu Meet Assoc Res Vision Ophthalmol (April 29-May4, Fort Lauderdale) 2001, Abst.
9. Chen, J. et al. *Pharmacological characterization of AGN 192024 (Lumigan(TM)) in ocular and non-ocular preparations and its relation to the prostamides.* Annu Meet Assoc Res Vision Ophthalmol (April 29-May4, Fort Lauderdale) 2001, Abst.

PHOTOSENSITIZERS

301352

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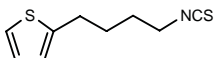
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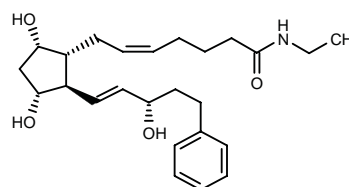
OCULAR MEDICATIONS

BIMATOPROST

251988

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TRAVOPROST⁺

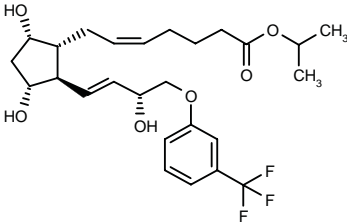
Prop INN; USAN

275677

7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

(+)-16-[3-(Trifluoromethoxy)phenoxy]-17,18,19,20-tetranorprostaglandin F_{2α} isopropyl ester

(+)-Fluprostenol isopropyl ester
AL-6221



C26 H35 F3 O6; Mol wt: 500.5505

ACTION – Selective prostanoid FP receptor agonist, a synthetic PGF_{2α} analogue.

INDICATION – Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or are insufficiently responsive.

PRESENTATION – Ophthalmic solution, 0.004%.

PROPRIETARY NAME – Travatan (US).

SOURCE – Alcon.

REFERENCES

1. Klimko, P.G. et al. (Alcon Laboratories, Inc.) *Use of cloprostenol, fluprostenol and their analogues for the manufacture of a medicament for the treatment of glaucoma and ocular hypertension*. EP 0639563, JP 1995165703, JP 1998182465, US 5665773.

2. Schneider, L.W. (Alcon Laboratories, Inc.) *Storage-stable prostaglandin compsns*. AU 4649596, EP 0812198, US 5631287, WO 9729752.

3. Dean, T. et al. *Dose response studies with Travatan(TM) a new prostaglandin analog in patients with ocular hypertension or open-angle glaucoma*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 26.

4. Dean, T.R. et al. *Improvement of optic nerve head blood flow after one-week topical treatment with travoprost (AL06221) in the rabbit*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2688.

5. Garadi, R. et al. *Travoprost: A new once-daily dosed prostaglandin for the reduction of elevated intraocular pressure*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4378.

6. Hellberg, M. et al. *Preclinical efficacy of AL-6221, a potent and selective FP prostaglandin agonist*. Invest Ophthalmol Visual Sci 1998, 39(Suppl. 4): Abst 1961.

7. McCue, B. et al. *LC/API-electrospray MS determination of the prostaglandin F2-alpha derivative ester prodrug, AL-6221, and its active acid metabolite, AL-5848, in plasma from humans and laboratory animals*. 46th ASMS Conf Mass Spectrom Allied Top (May 31-June 4, Orlando) 1998, Abst.

8. Netland, P.A. *Comparison of the safety and efficacy of travoprost, latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 26.

9. Netland, P.A. et al. *IOP-lowering efficacy and safety of travoprost compared to latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

10. Orengo-Nania, S.D. et al. *Travoprost significantly decreased IOP in patients with open-angle glaucoma or ocular hypertension when used adjunctively with timolol*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

11. Orgul, S. *The safety and IOP lowering-efficacy of a new topical ocular prostaglandin analogue, travoprost (0.0015% and 0.004%), compared to timolol 0.5% in a nine-month multicenter study*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 26.

12. Robertson, S. and Silver, L.H. *Dose-response evaluation of travoprost ophthalmic solution (TravatanTM), a new topical ocular prostaglandin, in patients with open-angle glaucoma and ocular hypertension*. 12th Congr Eur Soc Ophthalmol (June 27-July 1, Stockholm) 1999, Abst FP153.

13. Robertson, S.M. et al. *Differences between black and non-black patients with open-angle glaucoma or ocular hypertension in IOP-lowering response to travoprost*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

14. Sallee, V. et al. *Correlation of results from preclinical experimental models used for evaluation of FP prostaglandin agonists for therapy of glaucoma*. Invest Ophthalmol Visual Sci 1998, 39(Suppl. 4): Abst 4274.

15. Selliah, R. et al. *Synthesis of [phenyl-2-H-3]-travoprost: Isopropyl ester prodrug of a selective prostaglandin FP receptor agonist*. J Label Compd Radiopharm 2001, 44(3): 173.

16. Sharif, N.A. et al. *[3H]AL-5848 ([3H]9β-(+)-fluprostenol). Carboxylic acid of travoprost (AL-6221), a novel FP prostaglandin to study the pharmacology and autoradiographic localization of the FP receptor*. J Pharm Pharmacol 1999, 51(6): 685.

17. Whitson, J.T. et al. *Travoprost, a new prostaglandin analogue, is superior to timolol in lowering IOP in patients with open-angle glaucoma or ocular hypertension*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

18. Woodward, D.F. and Chen, J. *Endothelium dependent, nitric oxide (NO) mediated vasorelaxation substantially contributes to ocular surface hyperemic responses produced by prostaglandin F2α (PGF2α) and its analogs*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 912.

19. *Development status update for antiglaucoma drug candidate*. DailyDrugNews.com (Daily Essentials) 1999, Oct 22.

20. *Proposed international nonproprietary names (Prop. INN): List 80*. WHO Drug Inf 1998, 12(4): 281.

21. *Travatan launch quickly follows first approval in U.S.* DailyDrugNews.com (Daily Essentials) 2001, April 4.

22. *Two new antiglaucoma drugs approved by FDA*. DailyDrugNews.com (Daily Essentials) 2001, March 19.

MONOGRAPH – Sorbera, L.A. and Castañer, J. *Travoprost*. Drugs Fut 2000, 25(1): 0041.

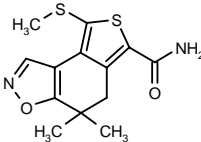
⁺Drug Data Rep 1999, 021(10): 0935.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

298408

4,4-Dimethyl-8-(methylsulfanyl)-4,5-dihydrothieno[3,4-*e*]-[1,2]benzisoxazole-6-carboxamide



C13 H14 N2 O2 S2; Mol wt: 294.3976

ACTION – Agent for the treatment or prevention of bone or nerve disorders proven to increase alkaline phosphatase, as well as to stimulate nodule induction in rat fetal parietal bone osteoblast cultures at a concentration of 0.3 µg/ml. Another compound from this series of dihydrobenz[c]thiophene derivatives is:

TRAVOPROST⁺

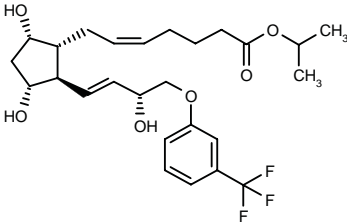
Prop INN; USAN

275677

7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

(+)-16-[3-(Trifluoromethoxy)phenoxy]-17,18,19,20-tetranorprostaglandin F_{2α} isopropyl ester

(+)-Fluprostenol isopropyl ester
AL-6221



C26 H35 F3 O6; Mol wt: 500.5505

ACTION – Selective prostanoid FP receptor agonist, a synthetic PGF_{2α} analogue.

INDICATION – Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or are insufficiently responsive.

PRESENTATION – Ophthalmic solution, 0.004%.

PROPRIETARY NAME – Travatan (US).

SOURCE – Alcon.

REFERENCES

1. Klimko, P.G. et al. (Alcon Laboratories, Inc.) *Use of cloprostenol, fluprostenol and their analogues for the manufacture of a medicament for the treatment of glaucoma and ocular hypertension*. EP 0639563, JP 1995165703, JP 1998182465, US 5665773.

2. Schneider, L.W. (Alcon Laboratories, Inc.) *Storage-stable prostaglandin compsns*. AU 4649596, EP 0812198, US 5631287, WO 9729752.

3. Dean, T. et al. *Dose response studies with Travatan(TM) a new prostaglandin analog in patients with ocular hypertension or open-angle glaucoma*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 26.

4. Dean, T.R. et al. *Improvement of optic nerve head blood flow after one-week topical treatment with travoprost (AL06221) in the rabbit*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2688.

5. Garadi, R. et al. *Travoprost: A new once-daily dosed prostaglandin for the reduction of elevated intraocular pressure*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4378.

6. Hellberg, M. et al. *Preclinical efficacy of AL-6221, a potent and selective FP prostaglandin agonist*. Invest Ophthalmol Visual Sci 1998, 39(Suppl. 4): Abst 1961.

7. McCue, B. et al. *LC/API-electrospray MS determination of the prostaglandin F2-alpha derivative ester prodrug, AL-6221, and its active acid metabolite, AL-5848, in plasma from humans and laboratory animals*. 46th ASMS Conf Mass Spectrom Allied Top (May 31-June 4, Orlando) 1998, Abst.

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22. *Two new antiglaucoma drugs approved by FDA*. DailyDrugNews.com (Daily Essentials) 2001, March 19.

MONOGRAPH – Sorbera, L.A. and Castañer, J. *Travoprost*. Drugs Fut 2000, 25(1): 0041.

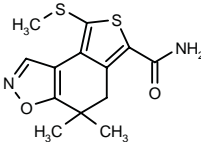
⁺Drug Data Rep 1999, 021(10): 0935.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

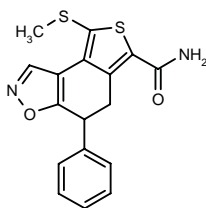
298408

4,4-Dimethyl-8-(methylsulfanyl)-4,5-dihydrothieno[3,4-*e*]-[1,2]benzisoxazole-6-carboxamide



C13 H14 N2 O2 S2; Mol wt: 294.3976

ACTION – Agent for the treatment or prevention of bone or nerve disorders proven to increase alkaline phosphatase, as well as to stimulate nodule induction in rat fetal parietal bone osteoblast cultures at a concentration of 0.3 µg/ml. Another compound from this series of dihydrobenz[c]thiophene derivatives is:



298409: C17 H14 N2 O2 S2

SOURCE – Taisho.

REFERENCES

1. Saito, S. et al. (Taisho Pharmaceutical Co., Ltd.) *Dihydrobenz[c]thiophene cpds.* JP 2000309591.

298524

N-Acetyl-L-arginyl-L-threonyl-L-glutaminyl-L-glutamyl-L-histidyl-L-threonyl-L-alanyl-L-glutamyl-L-seryl-L-lysineamide

C49 H82 N18 O19; Mol wt: 1227.2940

ACTION – Bone growth-stimulating agent, as demonstrated *in vivo* in a rat model. A representative compound from a series of polypeptides derived by chemical modification of a second bone-stimulating factor involved in parathyroid hormone (PTH) effects isolated from a human cDNA library. Other specifically claimed peptides are:

N-Acetyl-L-arginyl-L-threonyl-L-glutaminyl-L-glutamyl-L-histidyl-L-threonyl-L-alanyl-L-glutamyl-L-alanyl-L-lysineamide

298525: C49 H82 N18 O18

N-Acetyl-L-arginyl-L-threonyl-L-glutaminyl-L-glutamyl-L-histidyl-L-threonyl-L-alanyl-L-glutamyl-L-tyrosyl-L-lysineamide

298526: C55 H86 N18 O19

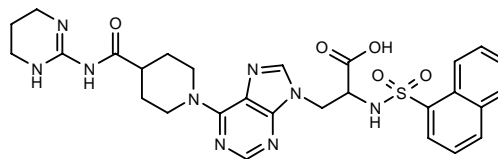
SOURCE – Osteopharm.

REFERENCES

1. Tam, C.S. (Osteopharm Inc.) *Bone stimulating factor.* WO 0075185.

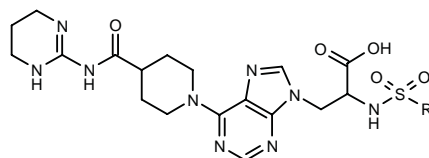
298722

2-(1-Naphthylsulfonamido)-3-[6-[4-[N-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]piperidin-1-yl]-9H-purin-9-yl]propionic acid



C28 H31 N9 O5 S; Mol wt: 605.6769

ACTION – Vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist, as demonstrated *in vitro* by inhibition of kistrin binding to the human vitronectin receptor ($IC_{50} = 1.9$ nM), as well as by inhibition of the binding of human vitronectin to human embryonic kidney 293 cells expressing $\alpha_v\beta_3$ ($IC_{50} = 30$ nM). In addition, compound inhibited osteoclast resorption in a pit assay with an IC_{50} value of 0.8 nM. Potentially useful for the treatment or prevention of bone disorders, particularly osteoporosis, as well as cancer, inflammatory disorders, cardiovascular diseases, restenosis, arteriosclerosis, nephropathies, retinopathies, psoriasis and rheumatoid arthritis. Other exemplified compounds from this series of substituted purine derivatives include the following:



Compound	R1	Formula
298723	2-Naph	C ₂₈ H ₃₁ N ₉ O ₅ S
298724	4-CF ₃ -Ph	C ₂₆ H ₂₈ F ₃ N ₉ O ₅ S
298725	2,4,6-(Me) ₃ -Ph	C ₂₇ H ₃₅ N ₉ O ₅ S

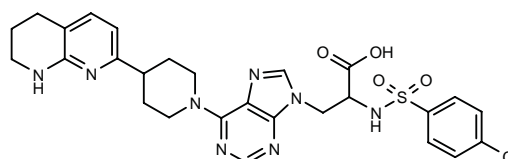
SOURCES – Aventis Pharma; Genentech.

REFERENCES

1. Knolle, J. et al. (Aventis Pharma Deutschland GmbH; Genentech, Inc.) *Substd. purine derivs. as inhibitors of cell adhesion.* EP 1065208, WO 0102399.

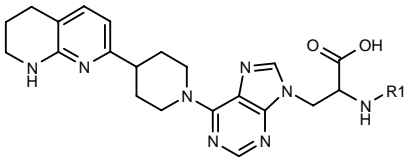
298726

2-(4-Chlorophenylsulfonamido)-3-[6-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)piperidin-1-yl]-9H-purin-9-yl]propionic acid



C27 H29 Cl N8 O4 S; Mol wt: 597.0971

ACTION – Vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist, as demonstrated *in vitro* by inhibition of kistrin binding to the human vitronectin receptor (IC_{50} = 5.1 nM), as well as by inhibition of the binding of human vitronectin to human embryonic kidney 293 cells expressing $\alpha_v\beta_3$ (IC_{50} = 15 nM). In addition, compound inhibited osteoclast resorption in a pit assay with an IC_{50} value of 0.3 nM. Potentially useful for the treatment or prevention of bone disorders, particularly osteoporosis, as well as cancer, inflammatory disorders, cardiovascular diseases, restenosis, arterio-sclerosis, nephropathies, retinopathies, psoriasis and rheumatoid arthritis. Other exemplified compounds from this series of naphthyridine derivatives include the following:



Compound	R1	Formula
298727	CO2CH2Ph	C ₂₉ H ₃₂ N ₆ O ₄
298728	SO2Ph	C ₂₇ H ₃₀ N ₆ O ₄ S
298729	1-Naph-SO2	C ₃₁ H ₃₂ N ₆ O ₄ S
298730	4-CF3-PhSO2	C ₂₈ H ₂₉ F ₃ N ₆ O ₄ S
298731	SO2Bu	C ₂₈ H ₃₄ N ₆ O ₄ S

SOURCES – Aventis Pharma; Genentech.

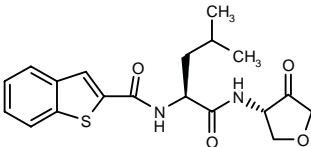
REFERENCES

1. Peyman, A. et al. (Aventis Pharma Deutschland GmbH;Genentech, Inc.) *Naphthyridine derivs., processes for their preparation, their use, and pharmaceutical compns. comprising them.* EP 1065207, WO 0102398.

299229

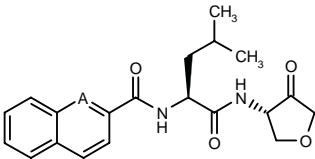
N-[3-Methyl-1 (*S*)-[*N*-[4-oxotetrahydrofuran-3 (*S*)-yl]-carbamoyl]butyl]benzothiophene-2-carboxamide

*N*²-(Benzothien-2-ylcarbonyl)-*N*¹-[4-oxotetrahydrofuran-3(*S*)-yl]-L-leucinamide



C19 H22 N2 O4 S; Mol wt: 374.4588

ACTION – Cathepsin K inhibitor (K_i = 8 nM) potentially useful for the treatment of diseases characterized by excessive bone loss such as osteoporosis. Other cyclic alkoxyketones include the following:



Compound	A	Formula
299230	CH	C ₂₁ H ₂₄ N ₂ O ₄
299231	N	C ₂₀ H ₂₃ N ₃ O ₄

SOURCE – GlaxoSmithKline.

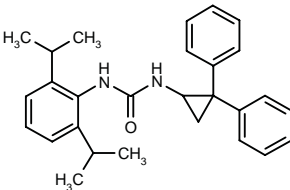
REFERENCES

1. Fenwick, A.E. et al. *Diastereoselective synthesis, activity and chiral stability of cyclic alkoxyketone inhibitors of cathepsin K.* Bioorg Med Chem Lett 2001, 11(2): 199.

TREATMENT OF LIPOPROTEIN DISORDERS

298065

N-(2,6-Diisopropylphenyl)-*N*'-(2,2-diphenylcyclopropyl)-urea



C28 H32 N2 O; Mol wt: 412.5738

ACTION – ACAT inhibitor with IC_{50} values of 17 and 141 nM, respectively, for inhibition of enzyme from hepatic microsomes from hypercholesterolemic rabbits and from rat peritoneal macrophages. It is expected to be useful for the treatment of hyperlipidemia and atherosclerosis.

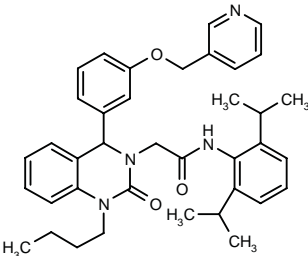
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Tanaka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Cycloalkyl derivs.* JP 2000290246.

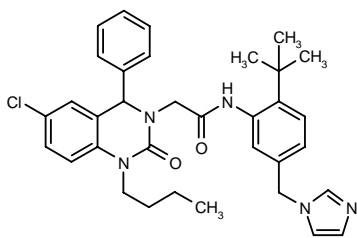
298273

2-[1-Butyl-2-oxo-4-[3-(3-pyridinylmethoxy)phenyl]-1,2,3,4-tetrahydroquinazolin-3-yl]-*N*-(2,6-diisopropylphenyl)-acetamide



C38 H44 N4 O3; Mol wt: 604.7906

ACTION – Agent for the treatment of hyperlipidemia and atherosclerosis with ACAT-inhibitory activity, as demonstrated *in vitro* by IC_{50} values of 3.5 and 70 nM, respectively, for inhibition of ACAT from rat peritoneal macrophages and from hepatic microsomes from hypercholesterolemic rabbits. Another compound from this series of quinazolinone derivatives is:



298274: C34 H38 Cl N5 O2

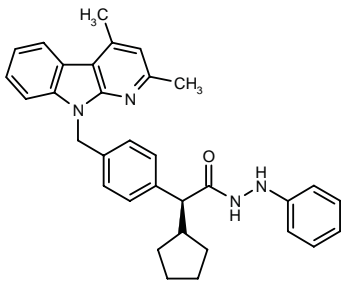
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Muraoka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel quinazolinone derivs.* JP 2000309576.

298439

2(*S*)-Cyclopentyl-2-[4-(2,4-dimethyl-9*H*-pyrido[2,3-*b*]indol-9-ylmethyl)phenyl]-*N*'-phenylacetohydrazide



C33 H34 N4 O; Mol wt: 502.6586

ACTION – Agent for the treatment of hyperlipidemia, arteriosclerosis, obesity and pancreatitis with apo B-associated lipoprotein secretion-inhibitory activity. *In vivo*, compound was found to reduce serum non-HDL cholesterol levels both in rats fed a high-fat diet and in LDL receptor-defective mice with ED₅₀ values of 0.15 and 1.8 mg/kg p.o., respectively. A representative compound from a series of hydrazide derivatives.

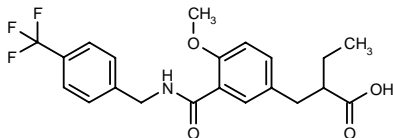
SOURCE – Yamanouchi.

REFERENCES

1. Suga, A. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Hydrazide derivs.* WO 0071502.

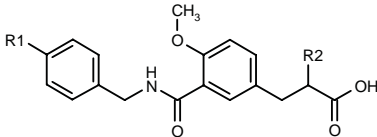
298465

2-[4-Methoxy-3-[*N*-[4-(trifluoromethyl)benzyl]carbamoyl]-benzyl]butyric acid



C21 H22 F3 N O4; Mol wt: 409.4018

ACTION – Lipid-lowering agent, a human peroxisome proliferator-activated receptor PPAR α agonist. *In vitro*, compound exhibited potent transcriptional activation effects in a luciferase reporter gene assay using CHO cells expressing the human receptor (EC₅₀ = 0.0115 μ M), as well as good binding affinity (EC₅₀ = 0.19 μ M). *In vivo*, it was shown to decrease free fatty acid, total cholesterol and plasma triglyceride levels by 77, 25 and 53%, respectively, in rats at 10 mg/kg/day p.o. x 4 days. Other exemplified compounds from this series of substituted phenylpropionic acid derivatives include the following:



Compound	R1	R2	Formula
298467	Ph	Et	C ₂₆ H ₂₇ NO ₄
298468	OPh	Et	C ₂₆ H ₂₇ NO ₅
298469	CF ₃	OMe	C ₂₀ H ₂₀ F ₃ NO ₅
298470	CF ₃	Me	C ₂₀ H ₂₀ F ₃ NO ₄
298471	4-F-PhO	Et	C ₂₆ H ₂₆ FNO ₅
298472	OPh	Pr	C ₂₇ H ₂₉ NO ₅
298473	4-F-PhO	Pr	C ₂₇ H ₂₈ FNO ₅

SOURCE – Kyorin.

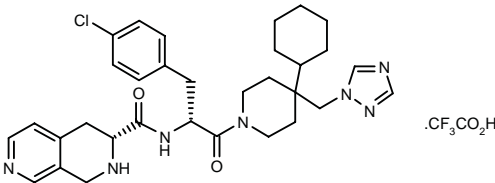
REFERENCES

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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

298734

N-[1(*R*)-(4-Chlorobenzyl)-2-[4-cyclohexyl-4-(1*H*-1,2,4-triazol-1-ylmethyl)piperidin-1-yl]-2-oxoethyl]-1,2,3,4-tetrahydro-2,7-naphthyridine-3(*R*)-carboxamide trifluoroacetate



C32 H40 Cl N7 O2 . C2 H F3 O2; Mol wt: 704.1899

ACTION – Potent and selective human melanocortin MC₄ receptor agonist, as demonstrated in binding assays by IC₅₀ values of 2100, > 10,000, 540, 0.92 and 230 nM, respectively, against [¹²⁵I]-NDP-α-MSH binding to MC₁, MC₂, MC₃, MC₄ and MC₅ receptors. *In vivo*, compound was effective in significantly increasing the number of erections in a conscious rat model of reflexogenic erections both i.v. (50% increase at 5.0 mg/kg 60 min after dosing) and p.o. (24% increase at 20 mg/kg 60 min after dosing). Potentially useful for the treatment or prevention of disorders responsive to activation of MC₄ receptors such as obesity, diabetes and sexual dysfunction, including erectile dysfunction and female sexual dysfunction. A representative compound from a series of substituted piperidines.

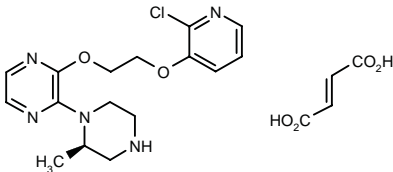
SOURCE – Merck & Co.

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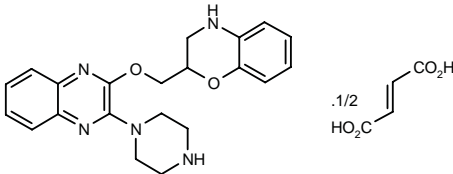
298865

2-[2-(2-Chloropyridin-3-yloxy)ethoxy]-3-[2(*R*)-methylpiperazin-1-yl]pyrazine fumarate

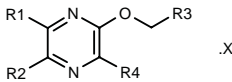


C16 H20 Cl N5 O2 . C4 H4 O4; Mol wt: 465.8916

ACTION – 5-HT_{2C} receptor modulator with a K_i of 5 nM in transfected HEK293 cells expressing the human receptor. Potentially useful for the treatment of 5-HT-related disorders such as obesity, memory disorders, schizophrenia, anxiety, mood disorders, pain, sexual dysfunction and urinary disorders. Other exemplified compounds include the following:



298873: C21 H23 N5 O2 . 1/2 C4 H4 O4



Compound	R1=R2	R3	R4	X	Formula
298866	H	2-Cl-PhOCH2	3-NH2-1-pyrrolidinyl		C ₁₆ H ₁₉ ClN ₄ O ₂
298867	H	3,5-(MeO)2-Ph-OCH2	1-Piz		C ₁₈ H ₂₄ N ₄ O ₄
298868	H	1-oxo-4-indanyl-OCH2	1-Piz		C ₁₉ H ₂₂ N ₄ O ₃
298869	H	2-Pyr-CH2CH2	1-Piz	fumarate	C ₁₆ H ₂₁ N ₅ O . C ₄ H ₄ O ₄
298870	H	2-benzofuryl	1-Piz	HCl	C ₁₇ H ₁₈ N ₄ O ₂ .HCl
298871	H	3-Pyr-OCH2	1-Piz	HCl	C ₁₅ H ₁₉ N ₅ O ₂ .HCl
298872	H	4-Pyr-OCH2	1-Piz	HCl	C ₁₅ H ₁₉ N ₅ O ₂ .HCl
298874	H	3-Pyr-OCH2	2(R)-Me-1-Piz	HCl	C ₁₆ H ₂₁ N ₅ O ₂ .HCl
298875	Me	CH2OPh	1-Piz	2HCl	C ₁₈ H ₂₄ N ₄ O ₂ ..2HCl
298876	H	3-(PhCH2O)-Ph-OCH2	1-Piz	CF3CO2H	C ₂₃ H ₂₆ N ₄ O ₃ .C ₂ HF ₃ O ₂

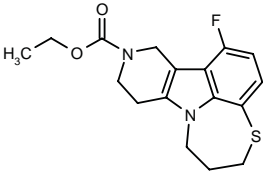
SOURCE – Pharmacia.

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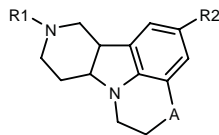
298908

1-Fluoro-6,7,9,10,11,12-hexahydro-5*H*-pyrido[4,3-*b*]-[1,4]thiazepino[2,3,4-*h*]indole-11-carboxylic acid ethyl ester



C17 H19 F N2 O2 S; Mol wt: 334.4131

ACTION – Agent for the treatment of CNS disorders including obesity, anxiety, depression, psychosis, schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, social phobias and gastrointestinal disorders such as gastrointestinal tract motility dysfunction, a 5-HT_{2A} and 5-HT_{2C} receptor modulator. A representative compound from a series of substituted heterocycle fused γ-carbolines, wherein the following are also included:



Compound	R1	R2	A	Formula
298909	CH2CH2CH=C(Me)2	H	-CH2S-	C ₂₀ H ₂₈ N ₂ S
298910	H	2-CF3-4-MeO-Ph	-CH2S-	C ₂₂ H ₂₃ F ₃ N ₂ OS
298911	(CH2)4CO2Et	H	-CH2S-	C ₂₁ H ₃₀ N ₂ O ₂ S
298912	4-F-PhCON(Me)CH2CH2	H	-CH2S-	C ₂₄ H ₂₈ FN ₂ OS
298913	6-F-3-indolyl-(CH2)3	H	-CH2S-	C ₂₅ H ₂₈ FN ₂ S
298914	H	N(Me)2	-CH2S-	C ₁₆ H ₂₃ N ₃ S
298915	H	4-Cl-Ph	-S-	C ₁₉ H ₁₉ ClN ₂ S
298916	H	2,3-(Cl)2-Ph	-CH2O-	C ₂₀ H ₂₀ Cl ₂ N ₂ O
298917	H	2-[MeCH(OH)]-4-F-Ph	-CH2S-	C ₂₂ H ₂₅ FN ₂ OS

SOURCE – DuPont Pharmaceuticals.

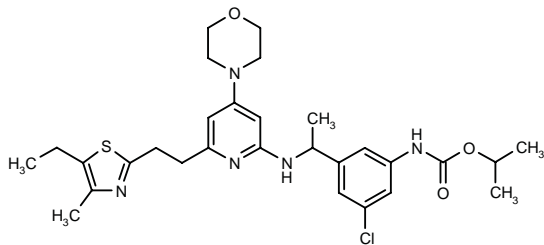
REFERENCES

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J-115814

300874

N-[3-Chloro-5-[1-[6-[2-(5-ethyl-4-methylthiazol-2-yl)ethyl]-4-(4-morpholinyl)pyridin-2-ylamino]ethyl]phenyl]carbamic acid isopropyl ester



C29 H38 Cl N5 O3 S; Mol wt: 572.1702

ACTION – Potent and selective neuropeptide Y (NPY) Y₁ antagonist with nanomolar binding affinity for the Y₁ receptor (K_i = 1.4, 1.8 and 1.9 nM for displacement of [¹²⁵I]-peptide YY binding to cell membranes expressing cloned human, rat and murine receptors, respectively) and low affinity for human Y₂, Y₄ and Y₅ receptors (K_i = 0.64, 6 and > 10 μM, respectively). Compound inhibited the NPY-induced increase in intracellular calcium levels in CHO cells expressing human Y₁ receptors (IC₅₀ = 6.8 nM) but did not induce an increase in intracellular Ca²⁺ at up to 1 μM. In satiated rats, it significantly and dose-dependently suppressed feeding induced by NPY after both intracerebroventricular (10-100 μg) and oral administration (0.3-30 mg). Moreover, compound significantly attenuated spontaneous feeding in *db/db* and lean C67BL6 mice when given i.p. (3-30 mg/kg). Potentially useful for the treatment of obesity.

SOURCE – Banyu.

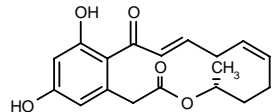
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Y5-02-B

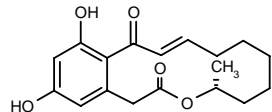
298066

(4*R*,7*Z*,10*E*)-13,15-Dihydroxy-4-methyl-2,4,5,6,9,12-hexahydro-1*H*-3-benzoxacyclotetradecin-2,12-dione



C18 H20 O5; Mol wt: 316.3510

ACTION – Antiobesity agent isolated from *Memnoniella subsimplex* RF-10104 (FERM P-17079) with affinity for neuropeptide Y (NPY) Y₅ receptors, as demonstrated by inhibition of [¹²⁵I]-peptide YY binding to human Y₅ receptors expressed in CHO cells (IC₅₀ = 0.02 mM) as well as by inhibition of forskolin-stimulated cAMP production in CHO cells expressing the human Y₅ receptor (IC₅₀ = 1.6 mM). Another compound isolated from the same source is:



Y5-02-C [298067]: C18 H22 O5

SOURCE – Shionogi.

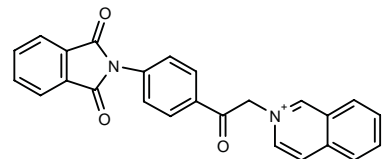
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HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

297888

2-[2-[4-(1,3-Dioxo-2,3-dihydro-1*H*-isoindol-2-yl)phenyl]-2-oxoethyl]isoquinolinium



C25 H17 N2 O3; Mol wt: 393.4203

ACTION – Agent for the treatment of sickle cell disease selected by screening sickle hemoglobin (HbS) ligands from a chemical library. It was found to be a potent inhibitor of HbS polymerization without affecting the oxygen-binding properties of HbS. *In vitro* assays using intact erythrocytes showed that this compound protected 67% of cells from sickling at a concentration of 1.05 mM.

SOURCE – Scriptgen.

REFERENCES

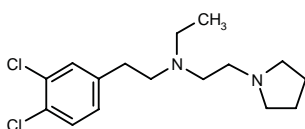
1. Corin, A.F. et al. (Scriptgen Pharmaceuticals, Inc.) *New anti-sickling agents: Selection methods and effective cpds.* US 6184228, WO 0071123.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

BD-1067

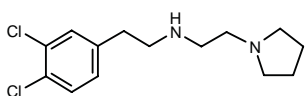
300536

N-[2-(3,4-Dichlorophenyl)ethyl]-*N*-ethyl-*N*-[2-(1-pyrrolidinyl)ethyl]amine



C16 H24 Cl2 N2; Mol wt: 315.2856

ACTION – σ Receptor ligand ($K_i = 2$ and 39 nM for binding to σ_1 and σ_2 receptors, respectively) with no affinity for dopamine D2, opioid, phencyclidine, GABA_A and 5-HT₂ receptors. In a functional assay of σ receptor activity, compound injected into the rat red nucleus significantly attenuated dystonia produced by the σ receptor agonist DTG. In addition, systemic pretreatment with BD-1067 (1-15 mg/kg i.p.) significantly reduced cocaine lethality in mice and both systemic (1-15 mg/kg i.p.) and intracerebroventricular (1-5 nmol) treatment with compound significantly reduced cocaine-induced convulsions. Potentially useful for counteracting the behavioral toxicity of cocaine. Another related analogue of BD-1008 is:



BD-1060 [300535]: C16 H20 Cl2 N2

SOURCES – National Institutes of Health, Bethesda, MD (US); University of Oklahoma Health Sciences Center, Oklahoma City, OK (US).

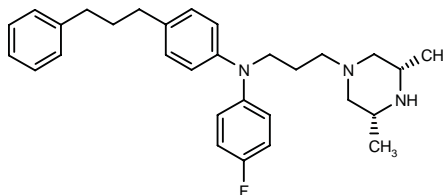
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3. Matsumoto, R.R. et al. *N-Alkyl substituted analogs of the sigma receptor ligand BD1008 and traditional sigma receptor ligands affect cocaine-induced convulsions and lethality in mice.* Eur J Pharmacol 2001, 411(3): 261.

JJC-1-059

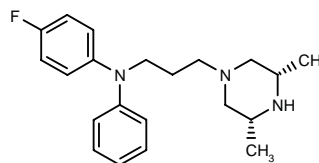
301826

cis-N-[3-(3,5-Dimethyl-1-piperazinyl)propyl]-4-fluoro-*N*-[4-(3-phenylpropyl)phenyl]aniline



C30 H38 F N3; Mol wt: 459.6492

ACTION – Selective ligand for the dopamine transporter (DAT; $K_i = 17.6$ nM) relative to the 5-HT (SERT; $K_i = 2132$ nM) or noradrenaline transporter (NET; $K_i = 1023$ nM), a rimcazole analogue with improved potency and selectivity ($K_i = 224$, 1710 and 3160 nM, respectively). Potentially useful for the treatment of cocaine abuse and addiction. Another compound within this series of rimcazole homologues is:



JJC-1-045 [301827]: C21 H28 F N3

SOURCE – National Institute on Drug Abuse, Bethesda MD (US).

REFERENCES

1. Ca, J. et al. *[3-cis-3,5-Dimethyl-1-piperazinyl]alkyl]-bis-(4'-fluorophenyl)amines analogs as novel probes for the dopamine transporter.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 96.

SOURCE – Scriptgen.

REFERENCES

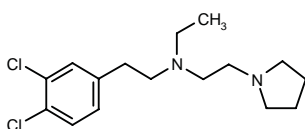
1. Corin, A.F. et al. (Scriptgen Pharmaceuticals, Inc.) *New anti-sickling agents: Selection methods and effective cpds.* US 6184228, WO 0071123.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

BD-1067

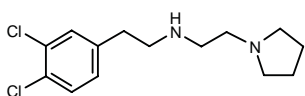
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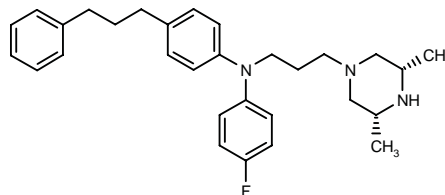
REFERENCES

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JJC-1-059

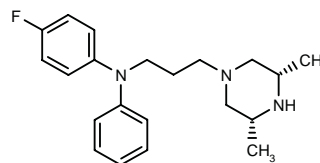
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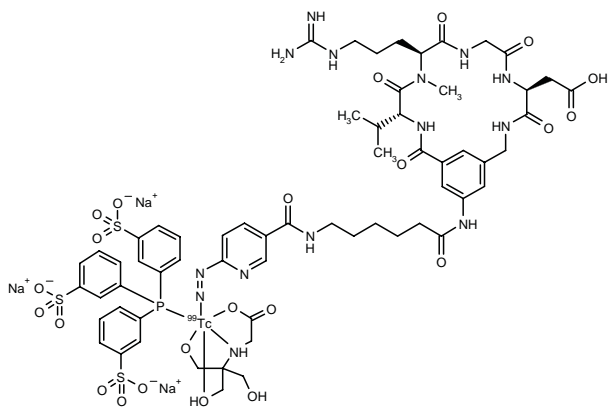
DIAGNOSTIC AGENTS

RP-444

224678

Trisodium hydrogen [cyclo[L-arginylglycyl-L-aspartyl-3-(aminomethyl)-5-[6-[6-(diazenyl-κN²)-3-pyridyl-carboxamido]hexanamido]benzoyl-D-valylato(2-)]][N-[2-hydroxy-1,1-bis[(hydroxy-κO)methyl]ethyl]glycinato(2-)-κN,κO][3,3',3''-(phosphinidyne-κP)tris(benzenesulfonato)-(3-)]technetate(4-)-99Tc

DMP-444
Tc-99m-DMP-444



C62 H75 N14 Na3 O23 P S3 Tc ; Mol wt: 1679.4910

ACTION – Radiopharmaceutical agent, a platelet gp IIb/IIIa receptor antagonist labeled with technetium-99m, suitable for diagnosis of deep vein thrombosis and pulmonary embolism. In a canine model of endothelial injury, it reliably detected acute platelet-rich thrombi 20-60 min after administration. Compound was also used for detecting acute infective endocarditis in dog, where clearly positive images were obtained early (1-4 h) after injection of the radiopharmaceutical. Currently under clinical investigation in patients with acute coronary syndromes.

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Edwards, D.S. and Liu, S. (DuPont Pharmaceuticals Co.) *Ternary radiopharmaceutical complexes*. EP 0995761, US 5744120, WO 9631243.

2. Barrett, J.A. et al. *DMP 444 a potential thrombus imaging agent*. J Nucl Med 1996, 37(5, Suppl.): Abst No. 508.

3. Crane, P.D. et al. *Canine distribution, metabolism and excretion of DMP 444, a potential thrombus imaging agent*. J Nucl Med 1996, 37(5, Suppl.): Abst No. 665.

4. Damphousse, D. et al. *DMP 444 a potential pulmonary emboli imaging agent*. J Nucl Med 1996, 37(5, Suppl.): Abst No. 466.

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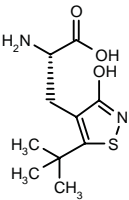
18. DuPont Merck Pharmaceutical Co. Annual Report 1994.

PHARMACOLOGICAL TOOLS

(S)-THIO-ATPA

294358

(+)-3-(5-*tert*-Butyl-3-hydroxyisothiazol-4-yl)-L-alanine
(+)-2(*S*)-Amino-3-(5-*tert*-butyl-3-hydroxyisothiazol-4-yl)propionic acid



C10 H16 N2 O3 S; Mol wt: 244.3134

ACTION – Potent and selective ionotropic glutamate AMPA GluR5 receptor agonist with submicromolar affinity (IC₅₀ = 0.27 μM) and little or no affinity for kainic and NMDA receptors (IC₅₀ = 14 and > 100 μM, respectively). Compound showed functional agonist activity at native AMPA receptors (EC₅₀ = 8.7 μM in rat cortical wedge preparations), as well as at cloned receptors, with higher potency at the GluR5 subtype (EC₅₀ = 0.10 μM) relative to GluR1, GluR3 and GluR4 subtypes (EC₅₀ = 5.2, 32 and 20 μM, respectively). Potentially useful as a tool to investigate the desensitization properties of AMPA receptors.

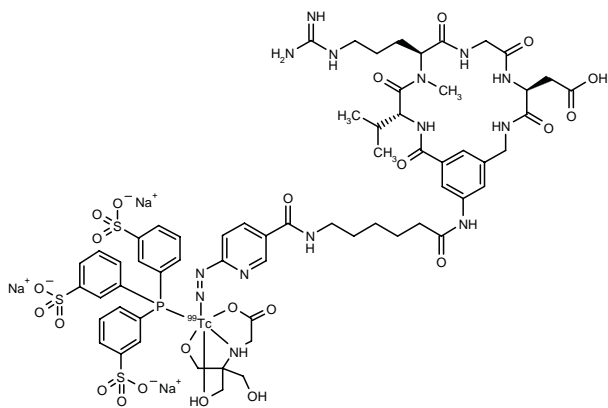
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5. Edwards, D.S. et al. *99mTc-Labeling of hydrazones of a hydrazinonicotinamide conjugated cyclic peptide*. Bioconjugate Chem 1999, 10(5): 803.

6. Edwards, D.S. et al. *New Tc-99m peptide conjugates based on a ternary ligand system*. J Nucl Med 1996, 37(5, Suppl.): Abst No. 105.

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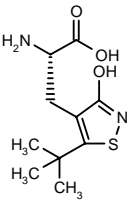
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PHARMACOLOGICAL TOOLS

(S)-THIO-ATPA

294358

(+)-3-(5-*tert*-Butyl-3-hydroxyisothiazol-4-yl)-L-alanine
(+)-2(*S*)-Amino-3-(5-*tert*-butyl-3-hydroxyisothiazol-4-yl)propionic acid



C10 H16 N2 O3 S; Mol wt: 244.3134

ACTION – Potent and selective ionotropic glutamate AMPA GluR5 receptor agonist with submicromolar affinity (IC₅₀ = 0.27 μM) and little or no affinity for kainic and NMDA receptors (IC₅₀ = 14 and > 100 μM, respectively). Compound showed functional agonist activity at native AMPA receptors (EC₅₀ = 8.7 μM in rat cortical wedge preparations), as well as at cloned receptors, with higher potency at the GluR5 subtype (EC₅₀ = 0.10 μM) relative to GluR1, GluR3 and GluR4 subtypes (EC₅₀ = 5.2, 32 and 20 μM, respectively). Potentially useful as a tool to investigate the desensitization properties of AMPA receptors.

SOURCES – University of Aarhus, Aarhus (DK); Royal Danish School of Pharmacy, Copenhagen (DK).

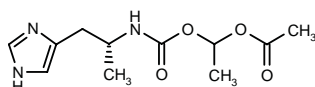
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299665

Acetic acid 1-[2-(1*H*-imidazol-4-yl)-1(*R*)-methylethylcarbamoyloxy]ethyl ester



C11 H17 N3 O4; Mol wt: 255.2723

ACTION – Prodrug of the histamine H₃ receptor agonist (*R*)- α -methylhistamine that undergoes complete hydrolysis to active compound *in vitro* under acidic conditions within 30 min. In mice, when prodrug was given orally at the dose of 24 μ mol/kg, high levels of active compound were detectable in plasma after 30 min and were sustained for 6 h; detectable drug concentrations were also found in cerebrospinal fluid. Lead compound for further prodrug development.

SOURCES – Freie Universität Berlin, Berlin (DE); INSERM, Paris Cedex (FR).

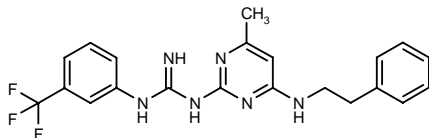
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GW-548118X

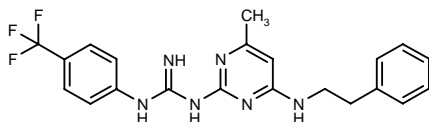
301693

N-[4-Methyl-6-(2-phenylethylamino)pyrimidin-2-yl]-*N'*-[3-(trifluoromethyl)phenyl]guanidine



C21 H21 F3 N6; Mol wt: 414.4329

ACTION – Neuropeptide Y (NPY) Y₅ antagonist (IC₅₀ = 20 nM), potentially useful as a tool to investigate the mechanisms underlying the effects of NPY on food intake. Another elated bisheteroaryl guanidine is:



GW-587081X [301692]: C21 H21 F3 N6

SOURCE – GlaxoSmithKline.

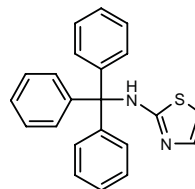
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UCL-2027

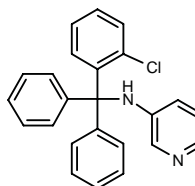
301015

N-(Triphenylmethyl)thiazol-2-amine



C22 H18 N2 S; Mol wt: 342.4642

ACTION – Clotrimazole analogue that selectively inhibits slow afterhyperpolarization in cultured hippocampal neurons (IC₅₀ = 1.1 μ M) while exerting only a marginal effect on SK1 and SK2 channels and no effect on Ca²⁺ currents. Potentially useful as a tool for establishing the physiological role of this current. Another clotrimazole analogue is:



UCL-1880 [301013]: C24 H19 Cl N2

SOURCE – University College London, London (GB).

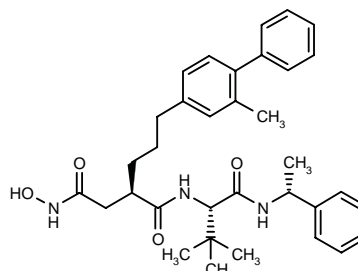
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UK-356618

300471

2(*R*)-[3-(2-Methylbiphenyl-4-yl)propyl]-*N*¹-[2,2-dimethyl-1(*S*)-[*N*-[1(*R*)-phenylethyl]carbamoyl]propyl]-*N*⁴-hydroxysuccinamide



C34 H43 N3 O4; Mol wt: 557.7307

ACTION – Potent matrix metalloproteinase MMP-3 (stromelysin 1) inhibitor ($IC_{50} = 5.9$ nM) with > 140-fold selectivity over MMP-1 (interstitial collagenase; $IC_{50} = 51,000$ nM), MMP-2 (gelatinase A; $IC_{50} = 1790$ nM), MMP-9 (gelatinase B; $IC_{50} = 840$ nM) and MMP-14 (MT1-MMP; $IC_{50} = 1900$ nM). Potentially useful as a tool for elucidating the pathological role of MMP-3.

SOURCE – Pfizer.

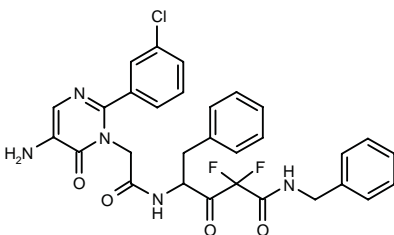
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Y-40018

300734

4-[5-Amino-2-(3-chlorophenyl)-6-oxo-1,6-dihydropyrimidin-1-ylacetamido]-N-benzyl-2,2-difluoro-3-oxo-5-phenylpentanamide



C30 H26 Cl F2 N5 O4; Mol wt: 594.0154

ACTION – Potent human chymase inhibitor ($K_i = 2.62$ nM) with 175-fold selectivity over chymotrypsin and at least 10-fold weaker activity against a range of other enzymes such as canine chymase, rat chymase, mouse chymase and human cathepsin G; moreover, compound was not active against human leukocyte elastase, human plasma thrombin and human angiotensin-converting enzyme (ACE). It was rapidly absorbed following oral administration in rats and dogs and exhibited an oral bioavailability of 17 and 32%, respectively. Potentially useful as a tool for elucidating the physiological and pathophysiological role of chymase and selected for further evaluation as a treatment for chymase-mediated diseases.

SOURCE – Welfide.

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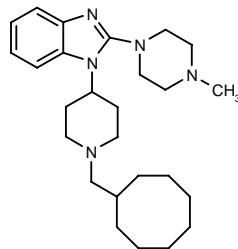
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**ANALGESIC AND ANESTHETIC
DRUGS**

ANALGESIC DRUGS

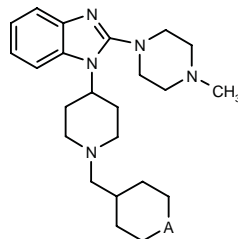
299319

1-[1-(Cyclooctylmethyl)piperidin-4-yl]-2-(4-methylpiperazin-1-yl)-1*H*-benzimidazole



C26 H41 N5; Mol wt: 423.6449

ACTION – Selective nociceptin N/OFQ (ORL-1) receptor agonist, potentially useful for the treatment of pain, inflammatory disorders and related conditions. Other specifically claimed 2-benzimidazolylamine compounds are:



Compound	A	Formula
299320	-CH2-	C ₂₄ H ₃₇ N ₅
299321	-(CH ₂) ₂ -	C ₂₅ H ₃₉ N ₅

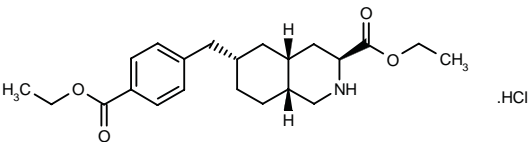
SOURCE – Pfizer.

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299675

(3*S*,4*aR*,6*S*,8*aR*)-6-(4-Ethoxycarbonylbenzyl)perhydroisoquinoline-3-carboxylic acid ethyl ester hydrochloride



C22 H31 N O4 . HCl; Mol wt: 409.9508

ACTION – Agent for the treatment of pain and migraine, a representative compound from a series of diester prodrugs of a known selective GluR5 receptor antagonist* that provide substantially improved bioavailability of the parent diacid and are substantially converted to the parent drug *in vivo*. In pharmacokinetic studies in rats, dogs and cynomolgus monkeys, compound exhibited oral bioavailabilities of 62.5%, 50.3% and 34.8%, respectively, when given at 10 mg/kg p.o., compared to values of 1.6%, 5.6% and 11.1% for the parent diacid drug at the same dose, which represents a 39-, 9- and 3.1-fold increase in oral bioavailability, respectively.

SOURCE – Lilly.

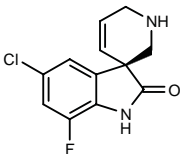
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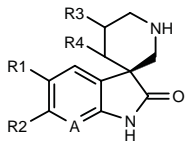
300365

(*S*)-5-Chloro-7-fluoro-1',2,2',3,3',6-hexahydrospiro[1*H*-indol-3,3'-pyridin]-2-one



C12 H10 Cl F N2 O; Mol wt: 252.6750

ACTION – Agent for the treatment of chronic pain reported to exhibit good analgesic properties in several animal models such as the formalin test in mice and the intraarticular Freund's complete adjuvant (FCA) test and the Chung nerve lesion test in rats. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
300368	Me	H	bond		N	C ₁₂ H ₁₃ N ₃ O
300369	Me	Me	bond		N	C ₁₃ H ₁₅ N ₃ O
300370	H	Me	bond		N	C ₁₂ H ₁₃ N ₃ O
300371	Cl	H	bond		N	C ₁₁ H ₁₀ ClN ₃ O
300372	F	H	bond		C(F)	C ₁₂ H ₁₀ F ₂ N ₂ O
300373	H	H	bond		C(Cl)	C ₁₂ H ₁₁ ClN ₂ O
300374	Me	H	bond		C(F)	C ₁₃ H ₁₃ FN ₂ O
300375	OMe	H	bond		CH	C ₁₃ H ₁₄ N ₂ O ₂
300376	Cl	H	H	H	CH	C ₁₂ H ₁₃ ClN ₂ O

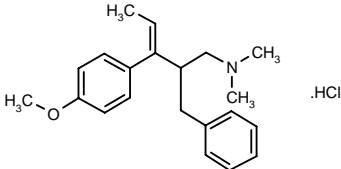
SOURCE – AstraZeneca.

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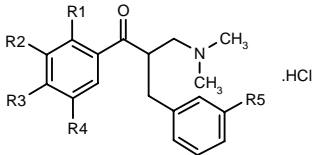
300417

2-Benzyl-3-(4-methoxyphenyl)-*N,N*-dimethyl-3(*Z*)-penten-1-amine hydrochloride



C21 H27 N O . HCl; Mol wt: 345.9112

ACTION – Analgesic agent, also reported to be useful for the treatment of urinary incontinence, inflammation, allergy, depression, drug and alcohol addiction, gastritis, diarrhea, cardiovascular disorders, respiratory disorders, cough, epilepsy and mental disorders. Analgesic activity was demonstrated by 100% inhibition of the phenyl-benzoquinone-induced writhing reaction in mice at 10 mg/kg i.v. Other exemplified compounds from this series of 3-amino-2-benzyl-1-phenylpropane derivatives include the following:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
300418	H	OCH2Ph	H	H	H		C ₂₅ H ₂₇ NO ₂ .HCl
300419	H	OH	H	H	H		C ₁₈ H ₂₁ NO ₂ .HCl
300420	H	OMe	H	OMe	H		C ₂₀ H ₂₅ NO ₃ .HCl
300421	OMe	H	H	OMe	H		C ₂₀ H ₂₅ NO ₃ .HCl
300422	H	OMe	H	H	Cl		C ₁₉ H ₂₂ ClNO ₂ .HCl
300423	H	OMe	H	H	H	S	C ₁₉ H ₂₃ NO ₂ .HCl
300424	Cl	H	H	Cl	H		C ₁₈ H ₁₉ Cl ₂ NO.HCl
300425	H	SMe	H	H	H		C ₁₉ H ₂₃ NOS.HCl
300426	H	H	H	CN	H		C ₁₉ H ₂₀ N ₂ O.HCl
300427	H	-CH=CHC(OH)=CH-	H	H	H		C ₂₂ H ₂₃ NO ₂ .HCl
300428	Me	Me	OMe	H	H		C ₂₁ H ₂₇ NO ₂ .HCl

SOURCE – Grünenthal.

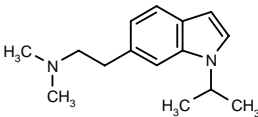
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ANTIMIGRAINE DRUGS

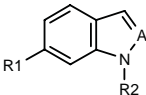
300294

N,N-Dimethyl-*N*-[2-(1-isopropyl-1*H*-indol-6-yl)ethyl]amine



C15 H22 N2; Mol wt: 230.3528

ACTION – Agent for the treatment of migraine with high affinity for 5-HT_{1D} receptors and selectivity over 5-HT_{1B} receptors. *In vitro*, compound gave > 90% inhibition of [³H]-5-HT binding to 5-HT_{1D} receptors at a concentration of 100 nM and was shown to decrease forskolin-stimulated cAMP production in CHO cells stably expressing the human 5-HT_{1D} receptor at 100 nM. Other compounds from this series of indole and indazole derivatives include the following:



Compound	R1	R2	A	Formula
300295	CH2CH2N(Me)2	i-Pr	N	C ₁₄ H ₂₁ N ₃
300296	1-Me-1,2,3,6-tetrahydro-4-Pyr	3-Pyr	CH	C ₁₉ H ₁₉ N ₃
300297	CH2CH2N(Me)2	3-thienyl	CH	C ₁₆ H ₁₈ N ₂ S

SOURCE – NPS Allelix.

REFERENCES

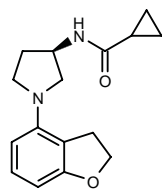
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

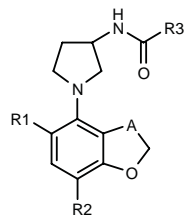
299825

N-[1-(2,3-Dihydrobenzofuran-4-yl)pyrrolidin-3(*R*)-yl]-cyclopropanecarboxamide



C16 H20 N2 O2; Mol wt: 272.3460

ACTION – Agent with melatonergic agonist activity (IC₅₀ < 10 nM for human MT₁ receptors expressed in NIH3T3 cells), potentially useful in the treatment of sleep disorders, circadian rhythm-related disorders, seasonal depression, melancholia, stress, appetite regulation, benign prostatic hyperplasia, inflammatory articular diseases, headache and related conditions. Other exemplified compounds from this series of heterocyclic aminopyrrolidine derivatives include the following:



Compound	R1	R2	R3	A	Isomer	Formula
299826	H	H	CH2OMe	-CH2-	S	C ₁₅ H ₂₀ N ₂ O ₃
299827	H	H	Et	-(CH2)2-	S	C ₁₆ H ₂₂ N ₂ O ₂
299828	H	H	NHEt	-CH2-	S	C ₁₅ H ₂₁ N ₃ O ₂
299829	H	H	NHEt	-CH2-	R	C ₁₅ H ₂₁ N ₃ O ₂
299830	Cl	Cl	Me	-CH2-	S	C ₁₄ H ₁₆ Cl ₂ N ₂ O ₂
299831	Cl	H	Pr	-CH2-	S	C ₁₆ H ₂₁ ClN ₂ O ₂

SOURCE – Bristol-Myers Squibb.

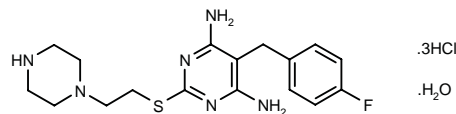
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ANXIOLYTICS

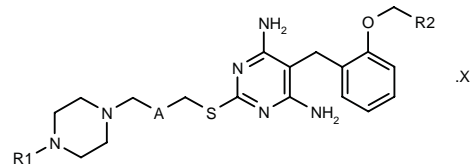
299325

5-(4-Fluorobenzyl)-2-[2-(1-piperazinyl)ethylsulfanyl]-pyrimidine-4,6-diamine trihydrochloride hydrate



C17 H23 F N6 S . 3HCl . H2O; Mol wt: 489.8722

ACTION – Anxiolytic agent that does not exert any action at 5-HT receptors and does not show sedative effects even at doses significantly higher than the anxiolytic dose. This compound displayed potent anxiolytic activity in the rat plus maze test with a minimum effective dose of 0.01 mg/kg p.o., compared to 1 mg/kg for diazepam. In a spontaneous motor activity test in mice, the compound had no effect even at a dose 14-fold higher than the ID₅₀ value for diazepam. It also has the advantage of not being metabolized. Other exemplified piperazinyl-alkylthiopyrimidine derivatives include the following:



Compound	R1	R2	A	X	Formula
299327	CH2CH2N(Me)2	H	bond	.4HCl .2H2O	C ₂₂ H ₃₆ N ₇ OS .4HCl.2H ₂ O
299328	CHO	Me	-CH2-		C ₂₁ H ₃₀ N ₆ O ₂ S
299329	(CH2)3N(Me)2	H	bond	.4HCl .H2O	C ₂₃ H ₃₇ N ₇ OS .4HCl.H ₂ O

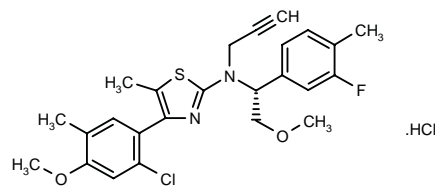
SOURCE – Egis.

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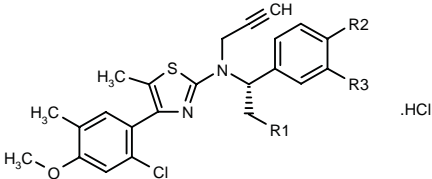
300356

4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[2-methoxy-1(*S*)-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)thiazol-2-amine hydrochloride



C25 H26 Cl F N2 O2 S . HCl; Mol wt: 509.4703

ACTION – Corticotropin-releasing factor (CRF) antagonist that is reported to be able to inhibit CRF-induced adrenocorticotropin (ACTH) secretion. It may be useful for the treatment of CRF-related disorders such as stress-related disorders, anxiety, depression, anorexia, epilepsy, fertility and sexual disorders, Alzheimer’s disease, etc. Other specifically claimed aminothiazole derivatives include the following:



Compound	R1	R2	R3	Formula
300357	cyclopropyl	F	H	C ₂₆ H ₂₆ ClFN ₂ OS.HCl
300358	Pr	CH ₂ OMe	H	C ₂₈ H ₃₃ ClN ₂ O ₂ S.HCl
300360	Pr	Me	F	C ₂₇ H ₃₀ ClFN ₂ OS.HCl
300361	cyclopropyl	Me	F	C ₂₇ H ₂₆ ClFN ₂ OS.HCl
300362	cyclopropyl	Cl	H	C ₂₆ H ₂₆ Cl ₂ N ₂ OS.HCl
300363	cyclopropyl	Br	H	C ₂₆ H ₂₆ BrClN ₂ OS.HCl
300364	Et	-OCH ₂ O-		C ₂₆ H ₂₇ ClN ₂ O ₃ S.HCl

SOURCE – Sanofi-Synthélabo.

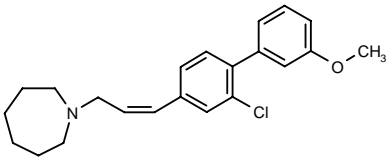
REFERENCES

1. Fontaine, E. et al. (Sanofi-Synthélabo) *Aminothiazole derivs. and their use as CRF receptor ligands*. FR 2796380, WO 0105776.

ANTIPSYCHOTIC DRUGS

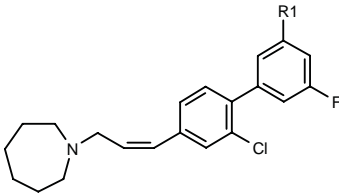
299676

1-[3-(2-Chloro-3'-methoxybiphenyl-4-yl)-2(Z)-propenyl]-perhydroazepine



C22 H26 Cl N O; Mol wt: 355.9064

ACTION – Antipsychotic agent that acts by specifically binding to σ receptors, particularly those of the central nervous system, and is reported to exhibit a low metabolism rate and/or to be devoid of significant interactions with cytochrome CYP 2D6. It is also reported to exhibit neuroprotective and analgesic properties and to be useful for the treatment of cardiovascular disorders, particularly for the regulation of heart rate. Other specifically claimed compounds from this series of cyclic *N*-aralkyl amine derivatives are:



Compound	R1	Formula
299677	H	C ₂₁ H ₂₃ ClFN
299678	F	C ₂₁ H ₂₂ ClF ₂ N

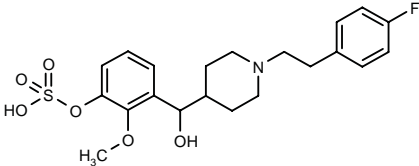
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Boigegrain, R. et al. (Sanofi-Synthélabo) *Antipsychotic cyclic N-aralkyl amines*. FR 2795724, WO 0102380.

300346

(±)-3-[1-[1-[2-(4-Fluorophenyl)ethyl]piperidin-4-yl]-1-hydroxymethyl]-2-methoxyphenyl hydrogen sulfate



C21 H26 F N O6 S; Mol wt: 439.5014

ACTION – 5-HT_{2A} receptor antagonist reported to be able to cross the blood–brain barrier, a metabolite of the known 5-HT_{2A} antagonist MDL-100907⁺. Potentially useful in the treatment of a broad range of disorders such as schizophrenia, anxiety, variant angina, anorexia nervosa, Raynaud’s phenomenon, intermittent claudication, coronary and peripheral vasospasm, fibromyalgia, cardiac arrhythmias, thrombotic disorders, extrapyramidal symptoms associated with neuroleptic agents, depressive and bipolar disorders, obsessive–compulsive disorders, insomnia and sleep apnea.

SOURCE – Aventis Pharma.

REFERENCES

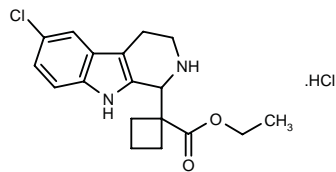
1. Bernotas, R. et al. (Aventis Pharmaceuticals, Inc.) *Sulfuric acid mono-[3-((1-[2-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl)-hydroxy-methyl)-2-methoxy-phenyl]ester*. WO 0105764.

⁺Drug Data Rep 1992, 014(10): 0858.

TREATMENT OF MOOD DISORDERS

299613

1-(6-Chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)cyclobutanecarboxylic acid ethyl ester hydrochloride



C18 H21 Cl N2 O2 . HCl; Mol wt: 369.2898

ACTION – A representative compound from a series of β -carboline derivatives, a 5-HT_{2C} and 5-HT_{2B} antagonist with potential for the treatment of depression, psychosis, schizophrenia, phobia, anxiety, panic attacks, sleep disorders, eating disorders, sexual disorders and migraine. Compound inhibited Ro-60-0175-induced penile erections in the rat with an ID₅₀ value of 0.9 mg/kg s.c.

SOURCE – ADIR.

REFERENCES

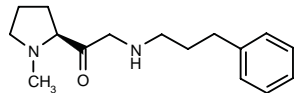
1. Goldstein, S. et al. (ADIR et Cie.) *β -Carboline derivs., process for their preparation and pharmaceutical compsns. containing them.* EP 1070716, FR 2796644, JP 2001072679.

NEUROLOGIC DRUGS

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

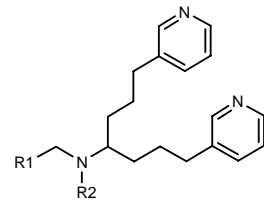
299860

1-[1-Methylpyrrolidin-2(S)-yl]-2-(3-phenylpropylamino)-ethanone

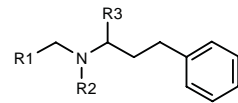


C16 H24 N2 O; Mol wt: 260.3786

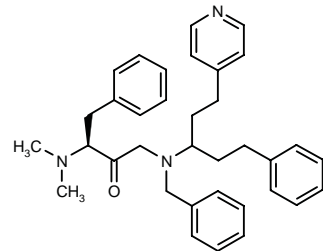
ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of amino-alkyl derivatives, wherein the following compounds are also included:



Compound	R1	R2	Formula
299861	N-Me-L-Pro-	Me	C ₂₅ H ₃₆ N ₄ O
299862	N-Et-L-Pro-	H	C ₂₅ H ₃₆ N ₄ O
299870	1-(PhCH2)-2(S)-Pip-COCH2	H	C ₃₂ H ₄₂ N ₄ O



Compound	R1	R2	R3	Formula
299863	1-Ac-2(S)-Pip-CO	H	H	C ₁₈ H ₂₆ N ₂ O ₂
299864	1-Me-2(S)-Pip-CO	2-thiazolyl-CH2	F	C ₂₁ H ₂₈ FN ₃ OS
299866	N,N-(Me)2-L-Phe-	H	H	C ₂₁ H ₂₈ N ₂ O
299869	1-Me-2(S)-Pip-COCH2	H	H	C ₁₈ H ₂₈ N ₂ O



299867: C35 H41 N3 O

SOURCE – Vertex.

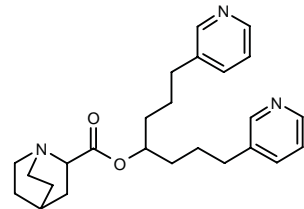
REFERENCES

1. Harbeson, S. and Mullican, M. (Vertex Pharmaceuticals Inc.) *Amino-alkyl derivs.* WO 0102376.

299871

1-Azabicyclo[2.2.2]octane-2-carboxylic acid 4-(3-pyridin-yl)-1-[3-(3-pyridinyl)propyl]butyl ester

Quinuclidine-2-carboxylic acid 4-(3-pyridinyl)-1-[3-(3-pyridinyl)propyl]butyl ester

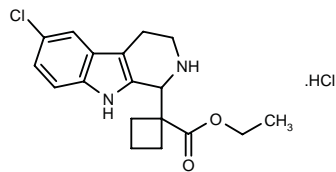


C25 H33 N3 O2; Mol wt: 407.5547

TREATMENT OF MOOD DISORDERS

299613

1-(6-Chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)cyclobutanecarboxylic acid ethyl ester hydrochloride



C18 H21 Cl N2 O2 . HCl; Mol wt: 369.2898

ACTION – A representative compound from a series of β -carboline derivatives, a 5-HT_{2C} and 5-HT_{2B} antagonist with potential for the treatment of depression, psychosis, schizophrenia, phobia, anxiety, panic attacks, sleep disorders, eating disorders, sexual disorders and migraine. Compound inhibited Ro-60-0175-induced penile erections in the rat with an ID₅₀ value of 0.9 mg/kg s.c.

SOURCE – ADIR.

REFERENCES

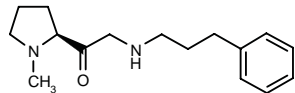
1. Goldstein, S. et al. (ADIR et Cie.) *β -Carboline derivs., process for their preparation and pharmaceutical compsns. containing them.* EP 1070716, FR 2796644, JP 2001072679.

NEUROLOGIC DRUGS

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

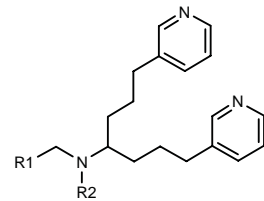
299860

1-[1-Methylpyrrolidin-2(*S*)-yl]-2-(3-phenylpropylamino)-ethanone

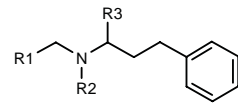


C16 H24 N2 O; Mol wt: 260.3786

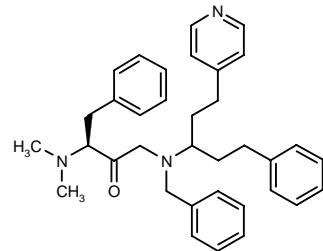
ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of amino-alkyl derivatives, wherein the following compounds are also included:



Compound	R1	R2	Formula
299861	N-Me-L-Pro-	Me	C ₂₅ H ₃₆ N ₄ O
299862	N-Et-L-Pro-	H	C ₂₅ H ₃₆ N ₄ O
299870	1-(PhCH2)-2(<i>S</i>)-Pip-COCH2	H	C ₃₂ H ₄₂ N ₄ O



Compound	R1	R2	R3	Formula
299863	1-Ac-2(<i>S</i>)-Pip-CO	H	H	C ₁₈ H ₂₆ N ₂ O ₂
299864	1-Me-2(<i>S</i>)-Pip-CO	2-thiazolyl-CH2	F	C ₂₁ H ₂₈ FN ₃ OS
299866	N,N-(Me)2-L-Phe-	H	H	C ₂₁ H ₂₈ N ₂ O
299869	1-Me-2(<i>S</i>)-Pip-COCH2	H	H	C ₁₈ H ₂₈ N ₂ O



299867: C35 H41 N3 O

SOURCE – Vertex.

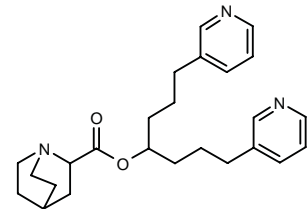
REFERENCES

1. Harbeson, S. and Mullican, M. (Vertex Pharmaceuticals Inc.) *Amino-alkyl derivs.* WO 0102376.

299871

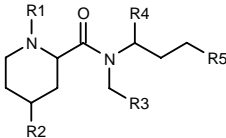
1-Azabicyclo[2.2.2]octane-2-carboxylic acid 4-(3-pyridin-yl)-1-[3-(3-pyridinyl)propyl]butyl ester

Quinuclidine-2-carboxylic acid 4-(3-pyridinyl)-1-[3-(3-pyridinyl)propyl]butyl ester

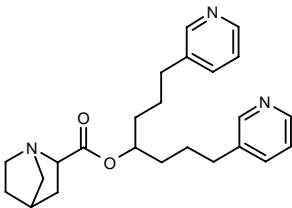


C25 H33 N3 O2; Mol wt: 407.5547

ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of quinuclidine derivatives, wherein the following compounds are also included:



Compound	R1,R2	R3	R4	R5	Formula
299872	-(CH2)2-	4-Pyr	H	Ph	C ₂₃ H ₂₉ N ₃ O
299873	-(CH2)2-	H	3-Pyr-(CH2)3	3-Pyr-CH2	C ₂₆ H ₃₆ N ₄ O
299876	-(CH2)-	4-Pyr	H	4-F-Ph	C ₂₂ H ₂₆ FN ₃ O
299877	-(CH2)-	Ph	3-Pyr-(CH2)3	3-Pyr-CH2	C ₃₁ H ₃₈ N ₄ O
299878	-(CH2)-	2-thiazolyl	H	Ph	C ₂₀ H ₂₅ N ₃ OS



299874: C₂₄ H₃₁ N₃ O₂

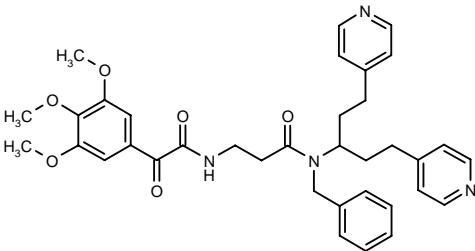
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REFERENCES

1. Lauffer, D. and Mullican, M. (Vertex Pharmaceuticals Inc.) *Quinuclidine derivs. for treatment of neurological disorders*. WO 0102405.

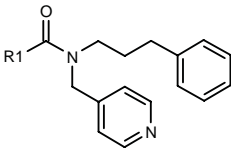
299879

N-Benzyl-3-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetamido]-*N*-[3-(4-pyridinyl)-1-[2-(4-pyridinyl)ethyl]propyl]propionamide



C₃₆ H₄₀ N₄ O₆; Mol wt: 624.7340

ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of β-amino acid derivatives, wherein the following compounds are also included:



Compound	R1	Formula
299880	3,4,5-(MeO)3-PhCOCONHCH2CH2	C ₂₉ H ₃₃ N ₃ O ₆
299881	2-[3,4,5-(MeO)3-PhCOCONH]-Ph	C ₃₃ H ₃₃ N ₃ O ₆
299883	2-[3,4,5-(MeO)3-PhCOCON(Me)]-Ph	C ₃₄ H ₃₆ N ₃ O ₆
299884	CH2CH2N(Et)2	C ₂₂ H ₃₁ N ₃ O

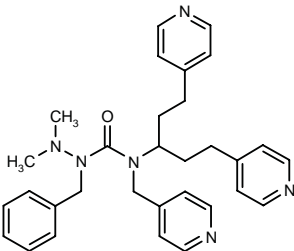
SOURCE – Vertex.

REFERENCES

1. Lauffer, D. and Mullican, M. (Vertex Pharmaceuticals Inc.) *Beta-amino acid derivs. for the treatment of neurological diseases*. WO 0102361.

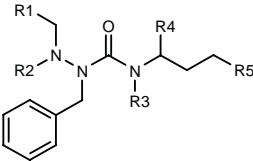
299885

2-Benzyl-1,1-dimethyl-4-(4-pyridinylmethyl)-4-[3-(4-pyridinyl)-1-[2-(4-pyridinyl)ethyl]propyl]semicarbazide

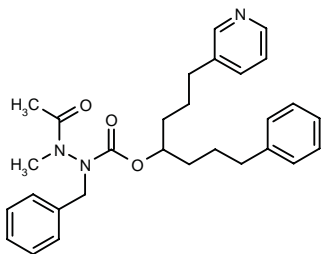


C₃₁ H₃₆ N₆ O; Mol wt: 508.6664

ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of azo amino acid derivatives, wherein the following compounds are also included:



Compound	R1	R2	R3	R4	R5	Formula
299886	Me	CH2Ph	4-Pyr-CH2	4-Pyr-CH2CH2	4-Pyr	C ₃₈ H ₄₂ N ₆ O
299888	Ph	CH2Ph	H	3-Pyr-(CH2)3	CH2Ph	C ₄₀ H ₄₄ N ₄ O
299889	H	COPh	Me	3-Pyr-(CH2)3	CH2Ph	C ₃₅ H ₄₀ N ₄ O ₂
299890	Ph	CO2CH2Ph	4-Pyr-CH2	H	Ph	C ₃₈ H ₃₈ N ₄ O ₃
299891	H	COCOPh	4-Pyr-CH2	H	4-F-Ph	C ₃₂ H ₃₁ FN ₄ O ₃
299892	H	CH2Ph	2-thiazolyl-CH2	H	Ph	C ₂₉ H ₃₂ N ₄ OS



299887: C29 H35 N3 O3

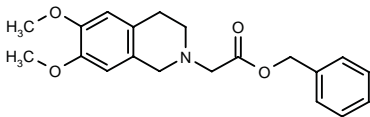
SOURCE – Vertex.

REFERENCES

1. Lauffer, D. and Mullican, M. (Vertex Pharmaceuticals Inc.) *Azo amino acid derivs. for the treatment of neurological diseases.* WO 0102362.

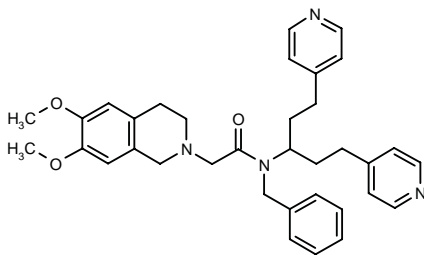
299893

2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetic acid benzyl ester



C20 H23 N O4; Mol wt: 341.4047

ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of *N*-heterocyclic derivatives, wherein the following compound is also included:



299894: C35 H40 N4 O3

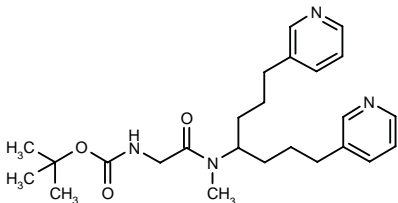
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REFERENCES

1. Lauffer, D. et al. (Vertex Pharmaceuticals Inc.) *N-Heterocyclic derivs. with neuronal activity.* WO 0102368.

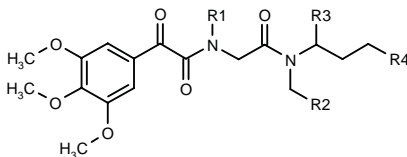
299895

*N*²-(*tert*-Butoxycarbonyl)-*N*¹-methyl-*N*¹-[4-(3-pyridyl)-1-[3-(3-pyridyl)propyl]butyl]glycinamide

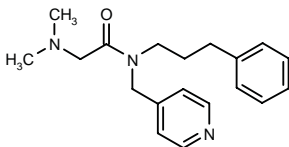


C25 H36 N4 O3; Mol wt: 440.5844

ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of *N*-substituted glycine derivatives, wherein the following compounds are also included:



Compound	R1	R2	R3	R4	Formula
299896	H	H	3-Pyr-(CH2)3	3-Pyr-CH2	C ₃₁ H ₃₈ N ₄ O ₆
299897	H	Ph	4-Pyr-CH2CH2	4-Pyr	C ₃₈ H ₃₈ N ₄ O ₆
299898	Me	Ph	4-Pyr-CH2CH2	4-Pyr	C ₃₈ H ₄₀ N ₄ O ₆
299899	Me	4-Pyr	H	Ph	C ₂₉ H ₃₃ N ₃ O ₆



299900: C19 H25 N3 O

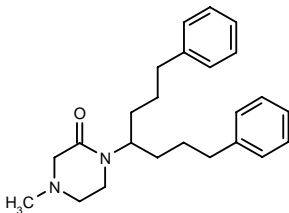
SOURCE – Vertex.

REFERENCES

1. Lauffer, D. et al. (Vertex Pharmaceuticals Inc.) *N-Substd. glycine derivs.* WO 0102363.

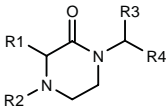
299901

4-Methyl-1-[4-phenyl-1-(3-phenylpropyl)butyl]piperazin-2-one



C24 H32 N2 O; Mol wt: 364.5298

ACTION – Neurotrophic agent for the treatment or prevention of neuronal damage associated with neurological diseases, particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. A representative compound from a series of cyclized amino acid derivatives, wherein the following compounds are also included:



Compound	R1	R2	R3=R4	Formula
299902	H	4-F-PhCH2	(CH2)3Ph	C ₃₀ H ₃₅ FN ₂ O
299903	Ph	CH2Ph	(CH2)3Ph	C ₃₆ H ₄₀ N ₂ O
299904	H	Me	CH2CH2Ph	C ₂₂ H ₂₈ N ₂ O
299905	H	4-F-PhCH2CH2	CH2CH2Ph	C ₂₉ H ₃₃ FN ₂ O
299906	Ph	CH2CH2Ph	CH2CH2Ph	C ₃₅ H ₃₈ N ₂ O
299907	H	Et	Ph	C ₁₉ H ₂₂ N ₂ O
299908	H	3,4,5-(MeO)3-PhCOCO	Ph	C ₂₈ H ₂₈ N ₂ O ₆
299909	Ph	3,4,5-(MeO)3-PhCOCO	Ph	C ₃₄ H ₃₂ N ₂ O ₆

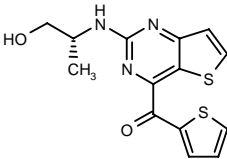
SOURCE – Vertex.

REFERENCES

1. Lauffer, D. and Ledford, B. (Vertex Pharmaceuticals Inc.) *Cyclized amino acid derivs.* WO 0102372.

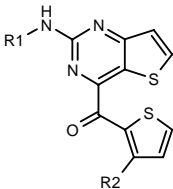
299969

1-[2-[2-Hydroxy-1 (*R*)-methylethylamino]thieno[3,2-*d*]-pyrimidin-4-yl]-1-(2-thienyl)methanone



C14 H13 N3 O2 S2; Mol wt: 319.4077

ACTION – Adenosine A_{2A} receptor antagonist proven to displace the radioligand [³H]-CGS-21680 from human adenosine A_{2A} receptors expressed in HEK-293 cells (K_i = 2 nM). The compound is useful for the treatment of movement disorders, particularly Parkinson’s disease. Other exemplified thieno- and furo-pyrimidine derivatives include the following:



Compound	R1	R2	Formula
299970	CH2CH2OH	H	C ₁₃ H ₁₁ N ₃ O ₂ S ₂
299971	(CH2)3CO2Et	H	C ₁₇ H ₁₇ N ₃ O ₃ S ₂
299972	CH(Me)CH2OH	H	C ₁₄ H ₁₃ N ₃ O ₂ S ₂
299973	CH2CH(OH)CH2OH	H	C ₁₄ H ₁₃ N ₃ O ₃ S ₂
299974	2-Pyr-CH2	H	C ₁₇ H ₁₂ N ₄ OS ₂
299975	(CH2)3OH	H	C ₁₄ H ₁₃ N ₃ O ₂ S ₂
299976	(S)-CH(Me)CH2OH	H	C ₁₄ H ₁₃ N ₃ O ₂ S ₂
299977	(R)-CH2CH(Me)OH	H	C ₁₄ H ₁₃ N ₃ O ₂ S ₂
299978	1-imidazolyl-(CH2)3	H	C ₁₇ H ₁₅ N ₅ O ₂ S ₂
299979	CH2CH2OH	Me	C ₁₄ H ₁₃ N ₃ O ₂ S ₂
299980	5-imidazolyl-CH2CH2	H	C ₁₆ H ₁₃ N ₅ O ₂ S ₂
299985	i-BuCONHCH2CH2	H	C ₁₈ H ₂₀ N ₄ O ₂ S ₂
299986	cyclohexyl-CONHCH2CH2	H	C ₂₀ H ₂₂ N ₄ O ₂ S ₂
299987	CH2CH2NHCO2Me	H	C ₁₅ H ₁₄ N ₄ O ₃ S ₂
299989	CH2CH2NHCO2CH2CH2Cl	H	C ₁₆ H ₁₅ ClN ₄ O ₃ S ₂
299990	allyl-NHCONHCH2CH2	H	C ₁₇ H ₁₇ N ₅ O ₂ S ₂

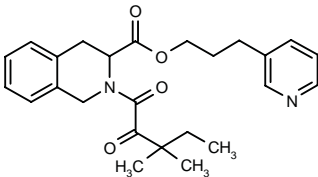
SOURCE – Vernalis Research.

REFERENCES

1. Gillespie, R.J. et al. (Vernalis Research Ltd.) *Thieno- and furopyrimidine derivs. as A_{2A}-receptor antagonists.* WO 0102409.

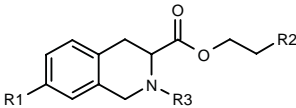
300250

2-(3,3-Dimethyl-2-oxopentanoyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid 3-(3-pyridinyl)propyl ester

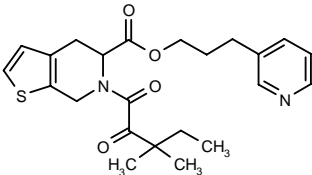


C25 H30 N2 O4; Mol wt: 422.5220

ACTION – Neurotrophic agent for the treatment or prevention of disorders characterized by neuronal damage such as Parkinson’s disease, Alzheimer’s disease, stroke, multiple sclerosis, amyotrophic lateral sclerosis, diabetic neuropathy, Bell’s palsy and spinal cord, brain or peripheral nerve trauma, proven to induce neurite outgrowth in rat dorsal root ganglion (DRG) cultures, in primary rat hippocampal cells and in human M17 neuroblastoma cells. In addition, compound exhibited *in vivo* activity in a rat facial nerve compression model, restoring whisker movement when given at 20 mg/kg p.o. b.i.d. x 15 days. Other specifically claimed compounds from this series of tetrahydroisoquinolines and tetrahydrothienopyridines are:



Compound	R1	R2	R3	Formula
300251	H	4-MeO-PhCH2CH2	COCOC(Me)2Et	C ₂₈ H ₃₅ NO ₅
300252	H	cyclohexyl-CH2	COCOC(Me)2Et	C ₂₆ H ₃₇ NO ₄
300253	H	CH(Ph)2	COCOC(Me)2Et	C ₃₂ H ₃₅ NO ₄
300254	H	3-Pyr-CH2	SO2CH2Ph	C ₂₅ H ₂₆ N ₂ O ₄ S
300255	H	3-Pyr-CH2	2-thienyl-COCO	C ₂₄ H ₂₂ N ₂ O ₄ S
300256	OMe	3-Pyr-CH2	COCOC(Me)2Et	C ₂₈ H ₃₂ N ₂ O ₅



300257: C23 H28 N2 O4 S

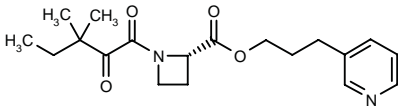
SOURCE – Ortho-McNeil.

REFERENCES

1. Macielag, M. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Neurotrophic tetrahydro-isoquinolines and tetrahydrothienopyridines, and related compsns. and methods.* WO 0104090.

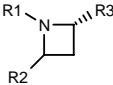
300258

1-(3,3-Dimethyl-2-oxopentanoyl)azetidine-2(S)-carboxylic acid 3-(3-pyridinyl)propyl ester



C19 H26 N2 O4; Mol wt: 346.4244

ACTION – Neurotrophic agent for the treatment or prevention of disorders characterized by neuronal damage such as Parkinson’s disease, Alzheimer’s disease, stroke, multiple sclerosis, amyotrophic lateral sclerosis, diabetic neuropathy, Bell’s palsy and spinal cord, brain or peripheral nerve trauma, proven to induce neurite outgrowth in rat dorsal root ganglion (DRG) cultures, in primary rat hippocampal cells and in human M17 neuroblastoma cells. In addition, compound exhibited *in vivo* activity in a rat facial nerve compression model, restoring whisker movement when given at 20 mg/kg p.o. b.i.d. x 15 days. Other specifically claimed compounds from this series of 2-azetidinecarboxylic acid derivatives are:



Compound	R1	R2	R3	Formula
300259	COCO-C(Me)2Et	H	3-Pyr-CH2CH2-C(Me)2OCO	C ₂₁ H ₃₀ N ₂ O ₄
300260	COCO-C(Me)2Et	H	CO2CH2-CH2CH(Ph)2	C ₂₆ H ₃₁ NO ₄
300261	t-BuNHCO	H	3-Pyr-(CH2)3OCO	C ₁₇ H ₂₅ N ₃ O ₃
300262	SO2CH2Ph	H	3-Pyr-(CH2)3OCO	C ₁₉ H ₂₂ N ₂ O ₄ S
300263	t-BuCOCO	H	3-Pyr-(CH2)3OCO	C ₁₈ H ₂₄ N ₂ O ₄
300264	1,5-(Me)2-3-pyrazolyl-CO	H	3-Pyr-(CH2)3OCO	C ₁₈ H ₂₂ N ₄ O ₃
300265	COCO-C(Me)2Et	H	1-[3-Pyr(CH2)3]-5-tetrazolyl	C ₁₉ H ₂₆ N ₆ O ₂
300266	COCOPh	(S)-4-MeO-Ph-(CH2)4OCO	4-MeO-Ph-(CH2)4OCO	C ₃₅ H ₃₉ NO ₈
300267	COCO-C(Me)2Et	(R)-3-Pyr-(CH2)3OCO	3-Pyr-(CH2)3OCO	C ₂₈ H ₃₅ N ₃ O ₆

SOURCE – Ortho-McNeil.

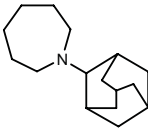
REFERENCES

1. Lanter, J.C. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Neurotrophic 2-azetidine-carboxylic acid derivs., and related compsns. and methods.* WO 0104091.

A-7

302298

1-(2-Adamantyl)perhydroazepine



C16 H27 N; Mol wt: 233.3963

ACTION – Adamantane derivative proven to be more effective than the parent compound and L-Dopa in animal models of Parkinson’s disease. Its activity appeared to be due in part to the ability to block NMDA receptor channels in rat hippocampal neurons (IC₅₀ = 11.8 μM). However, in this test compound showed efficacy comparable to adamantane but superior activity in animal models, indicating that the compound may have different effects on other channels or receptors, or different transport properties.

SOURCES – Institute of General Pathology & Pathophysiology, Moscow (RU); State University of New York, Stony Brook, Stony Brook, NY (US).

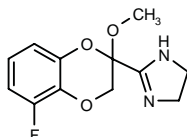
REFERENCES

1. Yelshansky, M.V. and Sobolevsky, A.I. *Blockade of open N-methyl-D-aspartate channels by a novel antiparkinsonian drug N-2-(adamantyl)hexamethylenimine.* 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst IV-PD-30.

TREATMENT OF DISORDERS OF COGNITION

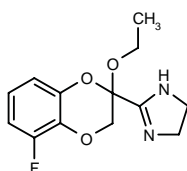
299349

(+)-2-(5-Fluoro-2-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl)-4,5-dihydro-1*H*-imidazole



C12 H13 F N2 O3; Mol wt: 252.2437

ACTION – Potent α_2 -adrenoceptor antagonist, potentially useful for the treatment or prevention of neurodegenerative disorders, attention deficit disorder, ischemic disorders, stroke, depression and male sexual dysfunction. Compound was shown to potently reverse the scopolamine-induced memory deficit in the dark avoidance assay in rats at 0.04-2.5 mg/kg, being comparable in potency to tacrine and more potent than donepezil, while the structurally related compound 2-methoxyidazoxan ([+]-RX-821002) was inactive. In addition, compound was found to be more potent than 2-methoxyidazoxan in inhibiting guanabenz-induced hypothermia following i.p. or p.o. administration, as well as in stimulating noradrenaline release in mice following i.p. administration. Another exemplified compound from this series of fluorinated imidazoline benzodioxane derivatives structurally related to idazoxan is:



299351: C13 H15 F N2 O3

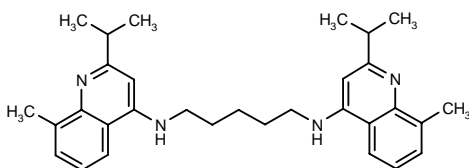
SOURCE – Pierre Fabre (bioMérieux-Pierre Fabre).

REFERENCES

1. Imbert, T. et al. (Pierre Fabre Médicament) *Novel fluorinated imidazoline benzodioxane, preparation and therapeutic uses thereof*. FR 2795727, WO 0100619.

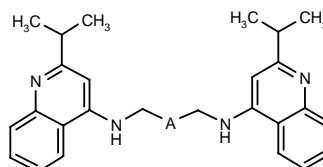
299604

N,N'-Bis(2-isopropyl-8-methylquinolin-4-yl)pentane-1,5-diamine



C31 H40 N4; Mol wt: 468.6850

ACTION – Agent for the treatment of neurodegenerative disorders, particularly dementia, that acts by blocking apamine-sensitive potassium channels. Compound was shown to inhibit Rb^+ efflux in PC12 cells (68% inhibition at 1 μ M). Also reported to be useful for the treatment of depression, mania, myotonic dystrophy, alcoholism, sleep disorders and bronchial asthma. Other specifically claimed compounds from this series of bis(quinolyl)-diamines are:



Compound	A	Formula
299605	-(CH ₂) ₃ -	C ₂₉ H ₃₆ N ₄
299606	-CH ₂ -	C ₂₇ H ₃₂ N ₄

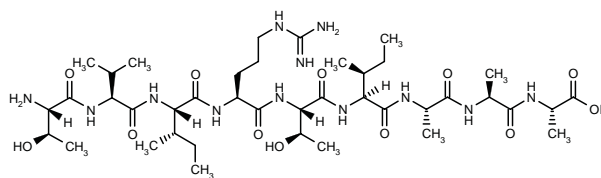
SOURCE – Bayer.

REFERENCES

1. Schohe-Loop, R. et al. (Bayer AG) *Bis-(quinolyl)-diamines*. US 6174897.

299856

L-Threonyl-L-valyl-L-isoleucyl-L-arginyl-L-threonyl-L-isoleucyl-L-alanyl-L-alanyl-L-alanine



C40 H74 N12 O12; Mol wt: 915.0966

ACTION – A representative compound from a series of short peptides that reduces the increase in the intracellular calcium concentration due to β -amyloid proteins β AP(25-35) and β AP(1-42) in hNT cells. This compound may be useful for alleviating the neurotoxic effects in Alzheimer's disease.

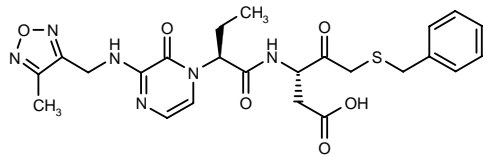
SOURCE – Massachusetts Institute of Technology, Cambridge, MA (US).

REFERENCES

1. Ingram, V.M. and Blanchard, B.J. (Massachusetts Institute of Technology) *Treatments for neurotoxicity in Alzheimer's disease caused by β amyloid peptides*. US 6172043.

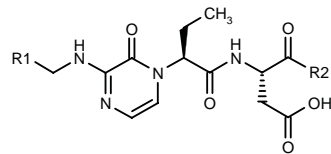
300395

5-(Benzylsulfanyl)-3(S)-[2(S)-[3-(4-methyl-1,2,5-oxadiazol-3-ylmethylamino)-2-oxo-1,2-dihydropyrazin-1-yl]butyramido]-4-oxopentanoic acid



C24 H28 N6 O6 S; Mol wt: 528.5872

ACTION – Caspase 3 inhibitor, potentially useful for the treatment of cardiac or cerebral ischemia, reperfusion injury, type 1 diabetes, AIDS, neuronal injury, neurodegenerative diseases and Parkinson’s disease, among others. Its use for the treatment of Alzheimer’s disease is specifically claimed. Other exemplified pyrazinones include the following:



Compound	R1	R2	Formula
300396	3-Me-1,2,4-oxadiazol-5-yl- -CH2CH2	CH2SCH2Ph	C ₂₆ H ₃₂ N ₆ O ₆ S
300397	2-oxo-1-pyrrolidinyl-CH2CH2	CH2SCH2Ph	C ₂₇ H ₃₅ N ₅ O ₆ S
300398	4-Me-1,2,5-oxadiazol-3-yl	1-pyrrolidinyl-CH2	C ₂₁ H ₂₉ N ₇ O ₆
300399	4-Me-1,2,5-oxadiazol-3-yl	H	C ₁₆ H ₂₀ N ₆ O ₆

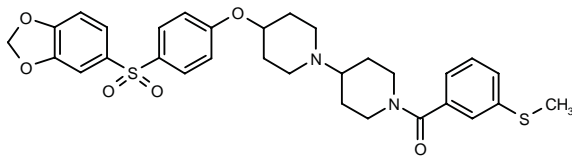
SOURCE – Merck Frosst.

REFERENCES

1. Han, Y. et al. (Merck Frosst Canada Inc.) *Pyrazinones, compsns. containing such cpds.* WO 0105772.

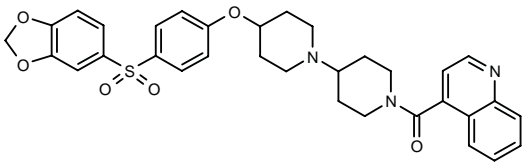
302636

4-[4-(1,3-Benzodioxol-5-ylsulfonyl)phenoxy]-1'-[3-(methylsulfanyl)benzoyl]-1,4'-bipiperidine



C31 H34 N2 O6 S2; Mol wt: 594.7496

ACTION – Muscarinic M₂ receptor antagonist with high binding affinity (K_i = 0.2 nM) and selectivity for M₂ over M₁ and M₃ receptors (ratios M₁/M₂ and M₃/M₂ = 234 and 109, respectively). Potentially useful for the treatment of Alzheimer’s disease. Another related compound is:



302634: C33 H33 N3 O6 S

SOURCE – Schering-Plough.

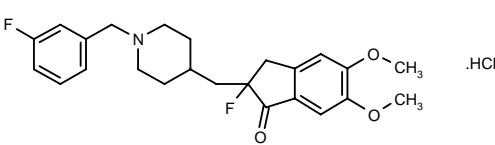
REFERENCES

1. Wang, Y. et al. *Design and synthesis of ether analogues as potent and selective M2 muscarinic receptor antagonists.* Bioorg Med Chem Lett 2001, 11(7): 891.

ER-127528*

294400

(+)-2-Fluoro-2-[1-(3-fluorobenzyl)piperidin-4-ylmethyl]-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one hydrochloride



C24 H27 F2 N O3 . HCl; Mol wt: 451.9382

ACTION – Acetylcholinesterase (AChE) inhibitor, a fluorine-containing derivative of donepezil with improved anti-AChE activity both *in vitro* (IC₅₀ = 0.2 and 3.9 nM, respectively) and *ex vivo* after oral administration in rats (IC₅₀ = 0.59 and 2.6 mg/kg, respectively). Potentially useful for the treatment of Alzheimer’s disease.

SOURCE – Eisai.

REFERENCES

1. Imura, Y. et al. (Eisai Co., Ltd.) *Fluorides of 4-substd. piperidine derivs.* JP 2000319258, WO 0051985.

2. Imura, Y. et al. *Recent advances in the study of acetylcholinesterase inhibitor "donepezil" (1): Synthesis and structure-activity relationships of fluorine-introduced donepezil and related compounds.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 67.

3. Imura, Y. et al. *Recent advances in the study of acetylcholinesterase inhibitor "donepezil": Synthesis and structure-activity relationships of fluorine-introduced donepezil and related compounds.* 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 1P-27.

4. Inoue, A. et al. *Recent advances in the study of acetylcholinesterase inhibitor "donepezil" (2): Docking simulations of fluorine-introduced donepezil with acetylcholinesterase.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 69.

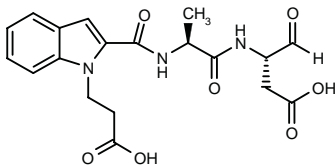
*Identified compound **294400** (see **294398**) Drug Data Rep 2001, 023(02): 0125.

TREATMENT OF
CEREBROVASCULAR DISEASES

299418

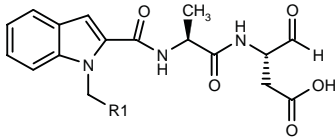
3(S)-[N-[1-(2-Carboxyethyl)-1*H*-indol-2-ylcarbonyl]-L-alanyl-amino]-4-oxobutyric acid

N-[1-(2-Carboxyethyl)-1*H*-indol-2-ylcarbonyl]-L-alanyl-L-aspart-1-al



C19 H21 N3 O7; Mol wt: 403.3889

ACTION – An inhibitor of the ICE/ced-3 family of cysteine proteases with potential for the treatment of inflammatory, autoimmune and neurodegenerative disorders and for the prevention of ischemic injury. *In vitro*, compound gave an IC₅₀ value of 0.198 μM against mICE compared to an IC₅₀ value of > 50 μM against CPP32. Other exemplified compounds from this series of C-terminal modified (N-substituted)-2-indolylcarbonyldipeptides include the following:



Compound	R1	Formula
299421	Ph	C ₂₃ H ₂₃ N ₃ O ₅
299715	H	C ₁₇ H ₁₉ N ₃ O ₅

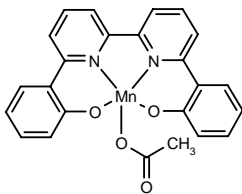
SOURCE – Idun Pharmaceuticals.

REFERENCES

1. Karanewsky, D.S. and Bai, X. (Idun Pharmaceuticals, Inc.) C-Terminal modified (N-substd.)-2-indolylcarbonyldipeptides as inhibitors of the ICE/CED-3 family of cysteine proteases. WO 0100658.

299601

(Acetato-κO)[[2,2'-([2,2'-bipyridine]-6,6'diyl-κN¹,κN^{1'})bis-phenolato-κO]](2-)]manganese



C24 H17 Mn N2 O4; Mol wt: 452.3463

ACTION – A representative compound from a series of bipyridine–manganese complexes effective as superoxide dismutase (SOD) and/or catalase (CAT) and/or peroxidase (POD) mimetics and which have antioxidant and/or free radical-scavenging activity. Compound was shown to be effective in a middle cerebral artery occlusion model in rats, giving 66.4% and 64.0% neuroprotection, respectively, when given at 1 mg/kg i.v. immediately before surgery or 3 h postsurgery. Potentially useful for the treatment or prevention of free radical-associated diseases or conditions including neurological disorders such as Alzheimer's disease and Parkinson's disease, cardiac tissue necrosis resulting from cardiac ischemia, autoimmune neurodegeneration (e.g., encephalomyelitis), acute lung injury such as sepsis and neuronal damage resulting from ischemia or trauma.

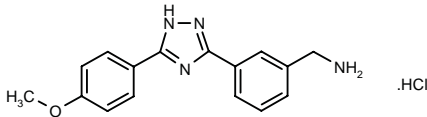
SOURCE – Eukarion.

REFERENCES

1. Campbell, I.B. et al. (Eukarion, Inc.) Bipyridine manganese complexes. US 6177419.

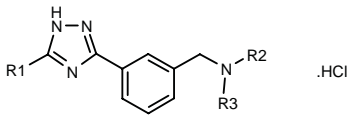
299617

3-[5-(4-Methoxyphenyl)-1*H*-1,2,4-triazol-3-yl]benzylamine hydrochloride



C16 H16 N4 O . HCl; Mol wt: 316.7903

ACTION – Agent for the treatment or prevention of diseases associated with overactivation of NMDA receptors including acute neurodegenerative disorders such as stroke and brain trauma, chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, as well as schizophrenia, anxiety, depression and pain, a selective antagonist of NMDA receptor subtypes. In a binding assay, compound exhibited an IC₅₀ value of 0.0083 μM against [³H]-Ro-25-6981 binding in rat brain membrane preparations. Other exemplified compounds from this series of triazole and imidazole derivatives include the following:



Compound	R1	R2	R3	Formula
299618	2-Naph	-(CH2)4-		C ₂₃ H ₂₃ ClN ₄
299619	4-Cl-Ph	-(CH2)4-		C ₁₉ H ₂₀ Cl ₂ N ₄
299620	4-MeO-Ph	-(CH2)4-		C ₂₀ H ₂₃ ClN ₄ O
299621	4-MeO-Ph	Et	Et	C ₂₀ H ₂₅ ClN ₄ O

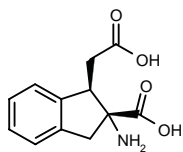
SOURCE – Roche.

REFERENCES

1. Alanine, A. et al. (F. Hoffmann-La Roche AG) Triazole and imidazole derivs. EP 1070708, JP 2001064263.

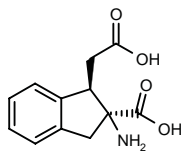
299679

trans-2-Amino-1-(carboxymethyl)-2,3-dihydro-1*H*-indene-2-carboxylic acid



C12 H13 N O4; Mol wt: 235.2377

ACTION – Agent for the treatment of CNS disorders, a potent antagonist of group II/III metabotropic glutamate receptors (GluRs), as demonstrated by an EC₅₀ value of 1.2 nM for inhibition of the glutamate-induced decrease in forskolin-induced cAMP accumulation in rat cortical slices. Compound was found to be a much weaker group I mGluR antagonist, as demonstrated by an EC₅₀ value of 2.2 μM for inhibition of the ACPD-induced increase in intracellular free inositol phosphate accumulation in neonatal rat tissue. Another exemplified compound from this series of 2-aminoindane derivatives is:



299680: C12 H13 N O4

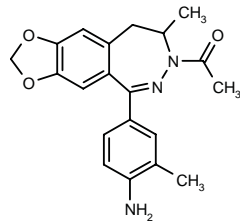
SOURCE – Prescient Neuropharma.

REFERENCES

1. Curry, K. (Prescient Neuropharma Inc.) *2-Aminoindane analogs*. WO 0102342.

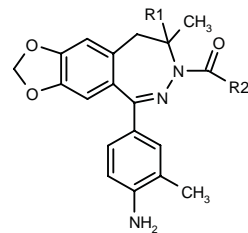
300082

(±)-1-[5-(4-Amino-3-methylphenyl)-8-methyl-8,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepin-7-yl]ethanone



C20 H21 N3 O3; Mol wt: 351.4039

ACTION – Noncompetitive AMPA/kainate receptor antagonist, potentially useful as a neuroprotectant, spasmolytic and muscle relaxant. Compound exhibited neuroprotective effects in an MgCl₂-induced global cerebral ischemia model in mice, giving a PD₅₀ value (dose that prolonged survival by 50%) of 5.4 mg/kg i.p. In addition, it was found to decrease body temperature in rats following i.p. administration, with a duration of action > 20 h. Other compounds from this series of substituted 1,3-dioxolo-[4,5-*h*][2,3]benzodiazepine derivatives include the following:



Compound	R1	R2	Formula
300083	CN	Me	C ₂₁ H ₂₀ N ₄ O ₃
300084	H	NHOMe	C ₂₀ H ₂₂ N ₄ O ₄

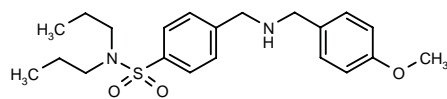
SOURCE – Egis.

REFERENCES

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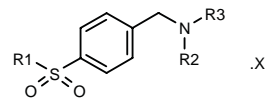
300213

4-(4-Methoxybenzylaminomethyl)-*N,N*-dipropylbenzene-sulfonamide

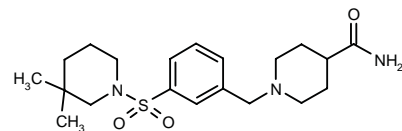


C21 H30 N2 O3 S; Mol wt: 390.5450

ACTION – An inhibitor of neuronal voltage-dependent calcium channels, potentially useful for the treatment of a broad range of disorders including anoxia, ischemia, stroke, heart failure, migraine, diabetes, cognitive impairment, pain, epilepsy, traumatic head or spinal injury, AIDS-related dementia, amnesia, neurodegenerative diseases, Down's syndrome, mood disorders, drug or alcohol addiction withdrawal, nausea from chemotherapy and carbon monoxide and cyanide poisoning. Other exemplified compounds from this series of sulfonamide substituted benzylamine derivatives include the following:



Compound	R1	R2	R3	X	Formula
300214	N(Pr)2	1-Pip-CH2CH2	3,4-(MeO)2-Ph-CH2CH2	2HCl	C ₃₀ H ₄₇ N ₃ O ₄ S .2HCl
300215	3,3-(Me)2- -1-Pip	H	4-Me-PhCH2		C ₂₂ H ₃₀ N ₂ O ₂ S
300216	3,3-(Me)2- -1-Pip	-CH2CH2CH(CH2Ph)CH2CH2-			C ₂₆ H ₃₆ N ₂ O ₂ S



300217: C20 H31 N3 O3 S

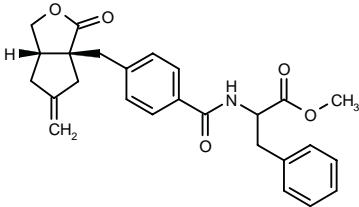
SOURCE – Lilly.

REFERENCES

1. Milutinovic, S.G. et al. (Eli Lilly and Company, Ltd.) *Sulfonamide subst. benzylamine derivs. and their use as medicaments*. WO 0104087.

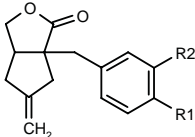
300218

2-[4-[(3a*S**,6a*S**)-5-Methylene-3-oxoperhydrocyclopenta[*c*]furan-3a-ylmethyl]benzamido]-3-phenylpropionic acid methyl ester



C26 H27 N O5; Mol wt: 433.5013

ACTION – Group I metabotropic glutamate receptor modulator with potential in the treatment of diseases caused by hyper- or hypofunction of the glutamatergic system, especially cerebral ischemia, cranial/cerebral trauma, pain and CNS-induced cramps. Other compounds from this series of substituted α,β -anellated butyrolactones include the following:



Compound	R1	R2	Formula
300219	(S)-NHCOCH(Ph)NH2	H	C ₂₃ H ₂₄ N ₂ O ₃
300220	2,3-dihydro-1,4-benzodioxin-6-yl-CH2CONH	H	C ₂₅ H ₂₅ NO ₅
300221	3-[N(Et)2CH2CH2O]-PhCH2CONH	H	C ₂₉ H ₃₆ N ₂ O ₄
300222	5-Cl-2-thienyl-SO2NH	H	C ₁₉ H ₁₈ ClNO ₄ S ₂
300223	cyclobutyl-CH2O	Br	C ₂₀ H ₂₃ BrO ₃
300224	NHCOCH2N(i-Bu)2	H	C ₂₅ H ₃₆ N ₂ O ₃
300225	3,4-(Me)2-PhCH2O	Cl	C ₂₄ H ₂₅ ClO ₃
300226	4-MeO-PhOCH2CH(OH)CH2NH	H	C ₂₅ H ₂₉ NO ₅
300227	5-N(CH2Ph)2-2-MeO-PhSO2NH	H	C ₃₆ H ₃₆ N ₂ O ₅ S
300228	i-PrOCH2CH(OH)CH2NH	H	C ₂₁ H ₂₉ NO ₄

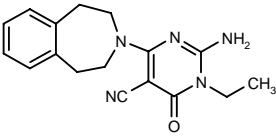
SOURCE – Bayer.

REFERENCES

1. Stolle, A. et al. (Bayer AG) *Substd. $\alpha\beta$ -anellated butyrolactones*. WO 0104107.

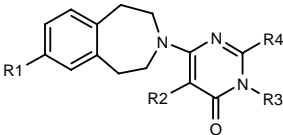
300561

2-Amino-1-ethyl-6-oxo-4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl)-1,6-dihydropyrimidine-5-carbonitrile

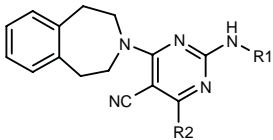


C17 H19 N5 O; Mol wt: 309.3711

ACTION – A representative compound from a series of 1,2,4,5-tetrahydrobenzo[*d*]azepines acting as group I metabotropic glutamate receptor (mGluR) antagonists. *In vitro*, compound displayed IC₅₀ values of 0.003 and 0.009 μ M, respectively, in a binding assay using HEK293 cells transiently transfected with the rat mGluR_{1a} receptor and in a functional assay using HEK-EBNA cells transiently transfected with the rat mGluR_{1a} receptor. Potentially useful in the treatment or prevention of acute and/or chronic neurological disorders including epilepsy, stroke, schizophrenia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, memory deficits, Parkinson's disease, spinal cord and head injuries, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia and retinopathy, as well as conditions that lead to glutamate deficiency functions such as muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychosis, anxiety, vomiting, dyskinesia and depression. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
300562	H	CN	OCH2CF3	Me	C ₁₈ H ₁₇ F ₃ N ₄ O ₂
300564	H	CN	Et	NHCHO	C ₁₈ H ₁₉ N ₅ O ₂
300565	H	CN	CH2CF3	Me	C ₁₈ H ₁₇ F ₃ N ₄ O
300567	H	CN	H	NHEt	C ₁₇ H ₁₉ N ₅ O
300568	H	NO2	CH2CF3	Me	C ₁₇ H ₁₇ F ₃ N ₄ O ₃
300569	H	CN	NHMe	Me	C ₁₇ H ₁₉ N ₅ O
300570	F	NO2	Et	Me	C ₁₇ H ₁₅ FN ₄ O ₃
300572	H	CN	H	Me	C ₁₆ H ₁₆ N ₄ O
300573	H	CN	-(CH2)3-		C ₁₈ H ₁₈ N ₄ O



Compound	R1	R2	Formula
300563	CH2CH2OH	OCH2CF3	C ₁₉ H ₂₀ F ₃ N ₅ O ₂
300566	H	SMe	C ₁₆ H ₁₇ N ₅ S
300571	4-morpholinyl-(CH2)3	OCH2CF3	C ₂₄ H ₂₅ F ₃ N ₆ O ₂

SOURCE – Roche.

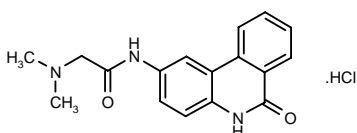
REFERENCES

1. Adam, G. et al. (F. Hoffmann-La Roche AG) *Tetrahydro-benzo(d)azepines and their use as antagonists at metabotropic glutamate receptors*. EP 1074549, JP 2001089472, US 6218385.

PJ-34

301919

2-(Dimethylamino)-*N*-(6-oxo-5,6-dihydrophenanthridin-2-yl)acetamide hydrochloride



C17 H17 N3 O2 . HCl; Mol wt: 331.8012

ACTION – Neuroprotective agent, a potent inhibitor of poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase; EC₅₀ = 20 nM in a cell-free PARP assay) proven to inhibit peroxynitrite-induced cell necrosis *in vitro* with an EC₅₀ value of 20 nM and oxygen–glucose deprivation-induced neuronal cell death in a concentration-related manner (30-1000 nM). In mice subjected to 1 h of middle cerebral artery occlusion followed by 23 h of reperfusion, compound (50 µg i.p.) given 2 h before MCAO and 6 h later reduced infarct volume by 48% compared to vehicle-treated controls. Similarly in rats, compound (10 mg/kg i.v.) given 10 min before 2 h of MCAO followed by 2 h of reperfusion induced a 70% reduction in infarct size. Marked neuroprotective effects were also seen in rats subjected to 2 h of occlusion and 22 h of reperfusion, where compound given shortly before occlusion induced a 90% reduction in infarct size. Other experiments demonstrated that the compound was able to protect against the development of endothelial dysfunction induced by high glucose concentrations *in vitro* and to restore normal vascular function in diabetes, despite the persistence of severe hyperglycemia and even after islet destruction had been initiated. Potentially useful for the treatment of stroke, as well as for improving vascular function in advanced diabetes.

SOURCE – Inotek.

REFERENCES

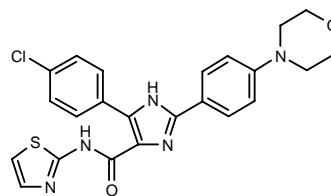
1. Abdelkarim, G.E. et al. *Protective effects of PJ34, a novel, potent inhibitor of poly(ADP-ribose) polymerase (PARP) in in vitro and in vivo models of stroke*. Int J Mol Med 2001, 7(3): 255.
2. Garcia Soriano, F. et al. *Anti-shock effects of novel phenanthridinone inhibitors of poly(ADP-ribose)polymerase*. FASEB J 2001, 15(4, Part 1): Abst 454.8.
3. Garcia Soriano, F. et al. *Diabetic endothelial dysfunction: The role of poly(ADP-ribose) polymerase activation*. Nat Med 2001, 7(1): 108.
4. Gertz, K. et al. *Neuroprotective effects of PJ34, a novel, potent inhibitor of poly (ADP-ribose) polymerase*. Soc Neurosci Abst 2000, 26(Part 1): Abst 286.1.
5. Mabley, J. et al. *Effect of novel poly (ADP-ribose)n polymerase (PARP) inhibitor in rodent models of local inflammation*. FASEB J 2001, 15(4, Part 1): Abst 217.10.
6. Virag, L. et al. *Cytoprotective effects of novel phenanthridinone inhibitors of poly(ADP-ribose) polymerase*. FASEB J 2001, 15(4, Part 1): Abst 461.9.

RESPIRATORY DRUGS

ASTHMA THERAPY

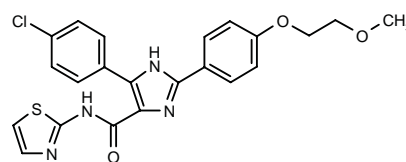
299265

5-(4-Chlorophenyl)-2-[4-(4-morpholinyl)phenyl]-*N*-(2-thiazolyl)-1*H*-imidazole-4-carboxamide



C23 H20 Cl N5 O2 S; Mol wt: 465.9630

ACTION – Agent for the treatment or prevention of allergic disorders such as atopic dermatitis, bronchial asthma and allergic rhinitis, a potent inhibitor of the production of IL-4 and IL-5 (IC₅₀ = 0.46 and 0.92 µM, respectively, in murine Th2 cells). *In vivo*, it was found to dose-dependently inhibit ovalbumin-induced ear edema at 0.3-3 mg/kg/day b.i.d. p.o. x 3 days in sensitized mice, and it further inhibited ovalbumin-induced eosinophil infiltration into bronchoalveolar lavage (BAL) in mice at 3 mg/kg p.o. Another compound from this series of imidazole derivatives is:



299266: C22 H19 Cl N4 O3 S

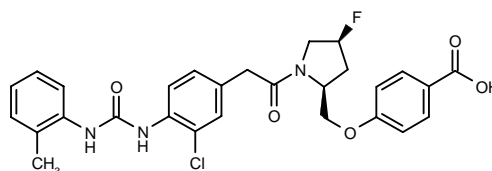
SOURCE – Welfide.

REFERENCES

1. Ehara, S. et al. (Welfide Corp.) *Novel imidazole derivs*. WO 0078758.

299378

4-[1-[2-[3-Chloro-4-[3-(2-methylphenyl)ureido]phenyl]-acetyl]-4(*S*)-fluoropyrrolidin-2(*S*)-ylmethoxy]benzoic acid



C28 H27 Cl F N3 O5; Mol wt: 539.9883

SOURCE – Roche.

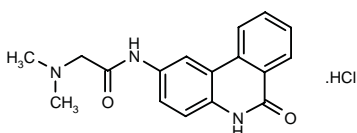
REFERENCES

1. Adam, G. et al. (F. Hoffmann-La Roche AG) *Tetrahydro-benzo(d)azepines and their use as antagonists at metabotropic glutamate receptors*. EP 1074549, JP 2001089472, US 6218385.

PJ-34

301919

2-(Dimethylamino)-*N*-(6-oxo-5,6-dihydrophenanthridin-2-yl)acetamide hydrochloride



C17 H17 N3 O2 . HCl; Mol wt: 331.8012

ACTION – Neuroprotective agent, a potent inhibitor of poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase; EC₅₀ = 20 nM in a cell-free PARP assay) proven to inhibit peroxynitrite-induced cell necrosis *in vitro* with an EC₅₀ value of 20 nM and oxygen–glucose deprivation-induced neuronal cell death in a concentration-related manner (30-1000 nM). In mice subjected to 1 h of middle cerebral artery occlusion followed by 23 h of reperfusion, compound (50 µg i.p.) given 2 h before MCAO and 6 h later reduced infarct volume by 48% compared to vehicle-treated controls. Similarly in rats, compound (10 mg/kg i.v.) given 10 min before 2 h of MCAO followed by 2 h of reperfusion induced a 70% reduction in infarct size. Marked neuroprotective effects were also seen in rats subjected to 2 h of occlusion and 22 h of reperfusion, where compound given shortly before occlusion induced a 90% reduction in infarct size. Other experiments demonstrated that the compound was able to protect against the development of endothelial dysfunction induced by high glucose concentrations *in vitro* and to restore normal vascular function in diabetes, despite the persistence of severe hyperglycemia and even after islet destruction had been initiated. Potentially useful for the treatment of stroke, as well as for improving vascular function in advanced diabetes.

SOURCE – Inotek.

REFERENCES

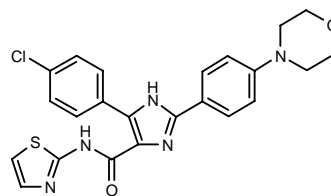
1. Abdelkarim, G.E. et al. *Protective effects of PJ34, a novel, potent inhibitor of poly(ADP-ribose) polymerase (PARP) in in vitro and in vivo models of stroke*. Int J Mol Med 2001, 7(3): 255.
2. Garcia Soriano, F. et al. *Anti-shock effects of novel phenanthridinone inhibitors of poly(ADP-ribose)polymerase*. FASEB J 2001, 15(4, Part 1): Abst 454.8.
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5. Mabley, J. et al. *Effect of novel poly (ADP-ribose)n polymerase (PARP) inhibitor in rodent models of local inflammation*. FASEB J 2001, 15(4, Part 1): Abst 217.10.
6. Virag, L. et al. *Cytoprotective effects of novel phenanthridinone inhibitors of poly(ADP-ribose) polymerase*. FASEB J 2001, 15(4, Part 1): Abst 461.9.

RESPIRATORY DRUGS

ASTHMA THERAPY

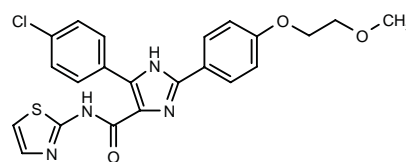
299265

5-(4-Chlorophenyl)-2-[4-(4-morpholinyl)phenyl]-*N*-(2-thiazolyl)-1*H*-imidazole-4-carboxamide



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299266: C22 H19 Cl N4 O3 S

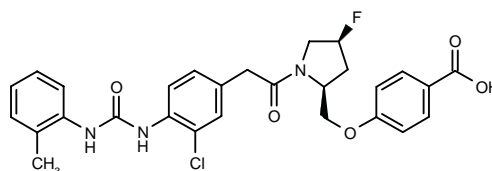
SOURCE – Welfide.

REFERENCES

1. Ehara, S. et al. (Welfide Corp.) *Novel imidazole derivs*. WO 0078758.

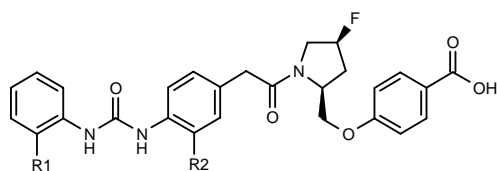
299378

4-[1-[2-[3-Chloro-4-[3-(2-methylphenyl)ureido]phenyl]-acetyl]-4(*S*)-fluoropyrrolidin-2(*S*)-ylmethoxy]benzoic acid



C28 H27 Cl F N3 O5; Mol wt: 539.9883

ACTION – A selective inhibitor of the binding of ligands to $\alpha_4\beta_1$ integrin (VLA-4), potentially useful in the treatment of conditions associated with VLA-4-mediated cell adhesion such as inflammatory and autoimmune disorders, diabetes, asthma, psoriasis, inflammatory bowel disease, transplant rejection and tumor metastasis. *In vitro*, compound gave a K_i value < 50 nM in a VLA-4 binding assay. *In vivo*, it was shown to dose-dependently inhibit eosinophil infiltration into BAL in sensitized mice at 10-50 mg/kg/day t.i.d. x 2 days, giving 45.9% inhibition at the 50 mg/kg dose; when administered i.v. at 30 mg/kg/day b.i.d. x 2 days, it gave 47.3% inhibition of eosinophil infiltration. In addition, it was shown to inhibit compound 48/80-induced eosinophil infiltration into the pleural cavity in rats following p.o. and i.v. administration (50.5% and 83.7% inhibition at 50 mg/kg/day p.o. x 2 days and 30 mg/kg/day i.v. x 2 days, respectively). Other exemplified compounds include the following:



Compound	R1	R2	Formula
299379	Br	Me	$C_{28}H_{27}BrFN_3O_5$
299380	Br	OMe	$C_{28}H_{27}BrFN_3O_6$
299381	Cl	Me	$C_{28}H_{27}ClFN_3O_5$

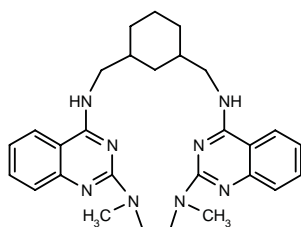
SOURCES – Daiichi Pharmaceutical; Pharmacopeia.

REFERENCES

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299821

20,23-Dimethyl-2,10,18,20,23,25,32,33-octaazahexacyclo[22.7.1.1^{4,8}.1^{11,19}.0^{12,17}.0^{26,31}]tetra-triaconta-1(32),11(33),12,14,16,18,24,26,28,30-decaene



C28 H34 N8; Mol wt: 482.6326

ACTION – Small-conductance Ca^{2+} -activated potassium SK channel blocker (IC_{50} < 1 μ M for inhibition of ionic current through rat SK2 channels expressed in HEK293 cells), with potential in the treatment or prevention of a broad range of conditions including asthma, cystic fibrosis, chronic obstructive pulmonary disease, convulsions, vascular and coronary artery spasms, renal diseases, urinary incontinence, irritable bowel syndrome, gastrointestinal dysfunction, cerebral and cardiac ischemia, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, anxiety, depression, dementia, Alzheimer's disease, dysmenorrhea, Ray-

naud's disease, migraine, arrhythmia, hypertension, type 2 diabetes, hyperinsulinemia, premature labor, baldness, cancer and immune suppression. A representative compound from a series of 2,4-bridged bis-4-aminopyrimidine derivatives and bridged bis-2-amino-benzimidazole derivatives.

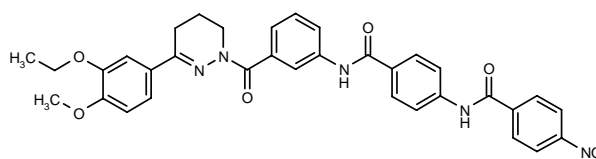
SOURCE – NeuroSearch.

REFERENCES

1. Teuber, L. et al. (NeuroSearch A/S) Potassium channel blocking agents. WO 0102406.

300131

N-[4-[N-[3-[3-(3-Ethoxy-4-methoxyphenyl)-1,4,5,6-dihydropyridazin-1-ylcarbonyl]phenyl]carbamoyl]phenyl]-4-nitrobenzamide



C34 H31 N5 O7; Mol wt: 621.6469

ACTION – Selective phosphodiesterase type 4 (PDE4) inhibitor also reported to inhibit TNF production, potentially useful for the treatment of allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis and other skin disorders, inflammatory diseases, autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis, osteoporosis, transplant rejection, cachexia, cancer, septicemia, memory impairment, atherosclerosis and AIDS. A specifically claimed compound from a series of benzoylpyridazines.

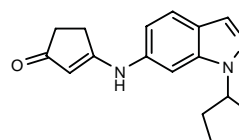
SOURCE – Merck KGaA.

REFERENCES

1. Jonas, R. et al. (Merck Patent GmbH) Benzoylpyridazines. DE 19932315, WO 0104099.

300148

3-(1-Cyclopentyl-1H-indazol-6-ylamino)-2-cyclopenten-1-one



C17 H19 N3 O; Mol wt: 281.3571

ACTION – Agent for the treatment of inflammatory and autoimmune diseases such as asthma, dermatitis, psoriasis, urticaria, multiple sclerosis and rheumatoid arthritis, a selective phosphodiesterase type 4 (PDE4) inhibitor reported to exhibit low toxicity.

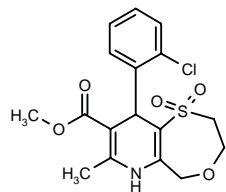
SOURCE – Nikken Chemicals.

REFERENCES

1. Ine, M. et al. (Nikken Chemicals Co., Ltd.) *Phosphodiesterase inhibitors*. JP 2001011047.

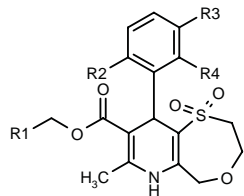
300237

9-(2-Chlorophenyl)-7-methyl-1,1-dioxo-2,3,6,9-tetrahydro-5H-[1,4]oxathiepino[6,5-*b*]pyridine-8-carboxylic acid methyl ester



C17 H18 Cl N O5 S; Mol wt: 383.8502

ACTION – Calcium channel antagonist proven to inhibit [³H]-nitrendipine binding in rabbit heart homogenates with an IC₅₀ value of 12 nM. Potentially useful for the treatment or prevention of a broad range of disorders including asthma, hypersensitivity, allergy, bronchospasm, dysmenorrhea, esophageal spasm, glaucoma, preterm labor, urinary tract disorders, gastrointestinal motility disorders and cardiovascular disorders such as hypertension, ischemia, angina, congestive heart failure, myocardial infarction and stroke. A representative compound from a series of oxathiepino[6,5-*b*]dihydropyridines, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
300238	CH2N(Me)CH2Ph	H	Cl	H	C ₂₆ H ₂₉ ClN ₂ O ₅ S
300239	CH2OCOPh	F	H	Cl	C ₂₅ H ₂₃ ClFNO ₇ S
300240	5-Me-2-oxo-1,3-dioxol-4-yl	H	Cl	Cl	C ₂₁ H ₁₉ Cl ₂ NO ₈ S

SOURCE – Ortho-McNeil.

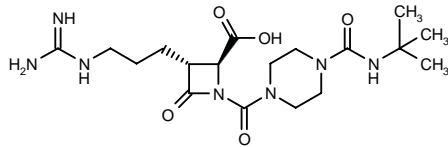
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1. Dodd, J.H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Oxathiepino[6,5-*b*]dihydropyridines, and related compsns. and methods*. WO 0104124.

BMS-262084*

284969

3(*R*)-(3-Guanidinopropyl)-1-[4-[*N*-(*tert*-butyl)carbamoyl]piperazin-1-ylcarbonyl]-4-oxoazetidine-2(*S*)-carboxylic acid



C18 H31 N7 O5; Mol wt: 425.4869

ACTION – Potent and selective tryptase inhibitor (IC₅₀ = 4 nM against human enzyme) proven to be effective in a guinea pig model of bronchoconstriction and lung inflammation. Potentially useful as an antiasthmatic agent.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Bisacchi, G. et al. (Bristol-Myers Squibb Co.) *Amidino and guanidino azetidinone tryptase inhibitors*. WO 9967215.

2. Qian, X. et al. *Efficient stereoselective synthesis of BMS-262084 an azetidinone-based tryptase inhibitor*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst ORGN 319.

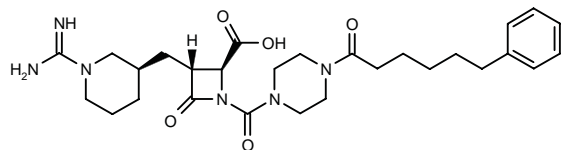
3. Sutton, J. et al. *Synthesis and SAR of 4-carboxy-2-azetidinone series of mechanism-based tryptase inhibitors*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 249.

*Identified compound **284969** Drug Data Rep 2000, 022(04): 0322.

BMS-363131

301775

3(*R*)-(1-Amidinopiperidin-3(*R*)-ylmethyl)-4-oxo-1-[4-(6-phenylhexanoyl)piperazin-1-ylcarbonyl]azetidine-2(*S*)-carboxylic acid



C28 H40 N6 O5; Mol wt: 540.6610

ACTION – Potent inhibitor of human tryptase (IC₅₀ < 2 nM) with > 1,500-fold selectivity over other serine proteases. Potentially useful for the treatment of allergic and inflammatory disorders such as asthma.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Bisacchi, G. et al. (Bristol-Myers Squibb Co.) *Amidino and guanidino azetidinone tryptase inhibitors*. WO 9967215.

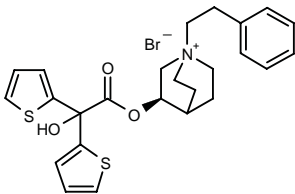
2. Slusarchyk, W.A. et al. *Design of potent and highly selective inhibitors of human tryptase*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 250.

TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY
DISEASES

300087

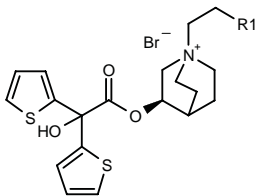
3(R)-[2-Hydroxy-2,2-di(2-thienyl)acetoxy]-1-(2-phenylethyl)-1-azoniabicyclo[2.2.2]octane bromide

3(R)-[2-Hydroxy-2,2-di(2-thienyl)acetoxy]-1-(2-phenylethyl)quinuclidinium bromide



C25 H28 Br N O3 S2; Mol wt: 534.5362

ACTION – Agent for the treatment of respiratory diseases such as chronic obstructive pulmonary disease, chronic bronchitis, asthma and rhinitis, urinary diseases such as urinary incontinence, pollakiuria, neurogenic bladder, nocturnal enuresis and chronic cystitis, and gastro-intestinal diseases such as irritable bowel syndrome, spastic colitis and diverticulitis, a potent muscarinic M₃ receptor antagonist (IC₅₀ = 2.7 nM against [³H]-NMS to human M₃ receptors cloned in CHO cells) with a long duration of action. Other compounds from this series of quinuclidine derivatives include the following:



Compound	R1	Formula
300088	CH2CH2Ph	C ₂₇ H ₃₂ BrNO ₃ S ₂
300089	2-thienyl	C ₂₃ H ₂₆ BrNO ₃ S ₃

SOURCE – Almirall Prodesfarma.

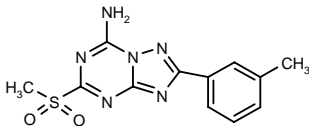
REFERENCES

1. Fernandez Forner, D. et al. (Almirall Prodesfarma, SA) *Novel quinuclidine derivs. and medicinal compns. containing the same*. WO 0104118.

AGENTS FOR RESPIRATORY
DISTRESS SYNDROME

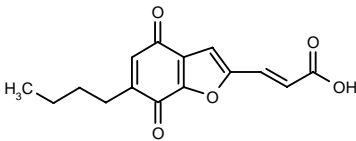
300120

2-(3-Methylphenyl)-5-(methylsulfonyl)[1,2,4]triazolo-[1,5-a][1,3,5]triazin-7-amine



C12 H12 N6 O2 S; Mol wt: 304.3328

ACTION – Agent for the treatment of a broad range of inflammatory disorders such as acute respiratory distress syndrome (ARDS), asthma, pneumonia, bronchitis, pancreatitis, arthritis, psoriasis, glomerulonephritis and tuberculosis, as well as hepatic or cerebral disorders, myocardial infarction, sepsis, arteriosclerosis and disseminated intravascular coagulation syndrome, proven to inhibit IL-8- or fMLP-induced migration of human neutrophils, as determined by inhibition of myeloperoxidase activity (IC₅₀ = 6 and 9 μM, respectively). In addition, compound was effective in a murine model of ARDS induced by lipopolysaccharide following i.v. administration, inhibiting neutrophil, lymphocyte and monocyte infiltration into the lungs, and it exhibited protective effects in a rat model of hepatic injury induced by ischemia of the hepatic artery at 1.14 mg/kg i.v. Compound also displayed protective effects against endotoxin-induced mortality in mice at 8.8 mg/kg i.v., inhibited ovalbumin-induced infiltration of eosinophils into bronchoalveolar lavage (BAL) in sensitized guinea pigs at 4.4 mg/kg i.v. and was effective in a murine model of delayed hypersensitivity, inhibiting ear edema formation by 36-48% at 8.8 mg/kg i.v. Another exemplified compound from this series of aromatic alkane derivatives is:



300121: C15 H14 O5

SOURCE – Eisai.

REFERENCES

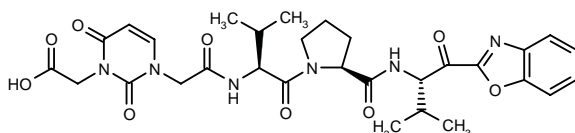
1. Sawai, T. et al. (Eisai Co., Ltd.) *Aromatic alkane derivs*. JP 2001011064.

BL-3730

302318

2-[N-[2-(3-Carboxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)acetyl]-L-valyl-L-prolyl-L-valyl]benzoxazole

2-[3-{2-[1(S)-[2(S)-[N-[1(S)-(Benzoxazol-2-ylcarbonyl)-2-methylpropyl]carbamoyl]-1-pyrrolidinylcarbonyl]-2-methylpropylamino]-2-oxoethyl]-2,6-dioxo-1,2,3,6-tetrahydro-1-pyrimidinyl]acetic acid



C30 H36 N6 O9; Mol wt: 624.6474

ACTION – Transition-state inhibitor of human neutrophil elastase (HNE; $IC_{50} = 24$ nM), a water-soluble peptide-based compound proven to inhibit HNE-induced lung hemorrhage in hamsters after both i.v. bolus and infusion ($ED_{50} = 3.4$ mg/kg and 1.5 mg/kg/h, respectively). Potentially useful for the treatment of acute respiratory distress syndrome, ischemia–reperfusion injury and multiple organ failure.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Sato, F. et al. (Dainippon Pharmaceutical Co., Ltd.) *Heterocyclic cpds., intermediates thereof and elastase inhibitors*. JP 2000256396, WO 0052032.

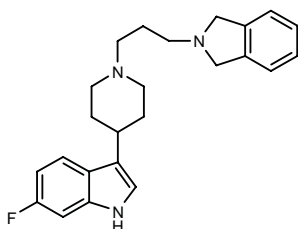
2. Inoue, Y. et al. *Design and synthesis of water-soluble novel cyclic amide-containing transition-state inhibitors of human neutrophil elastase*. 221st ACS Natl Meet (April 1–5, San Diego) 2001, Abst MEDI 242.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

299262

3-[1-[3-(2,3-Dihydro-1*H*-isoindol-2-yl)propyl]piperidin-4-yl]-6-fluoro-1*H*-indole



C24 H28 F N3; Mol wt: 377.5042

ACTION – Potent and selective α_{1B} -adrenoceptor antagonist, as demonstrated by K_i values of 0.79 and 24 nM, respectively, against [3H]-prazosin binding to α_{1B} - and α_{1A} -adrenoceptors from rat liver and rat mandibular gland. *In vivo*, compound was shown to dose-dependently (0.1–3 mg/kg/min i.v.) inhibit the phenylephrine-induced vasopressor response in rats, producing $86 \pm 2\%$ inhibition at 3 mg/kg/min. Potentially useful for the treatment of α_{1B} -adrenoceptor-related disorders, particularly hypertension. A representative compound from a series of indole derivatives.

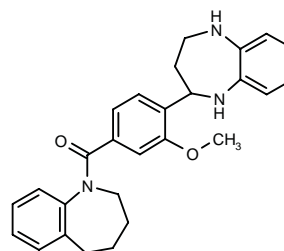
SOURCE – Toray.

REFERENCES

1. Hayasahi, R. et al. (Toray Industries, Inc.) *α_{1B} -Adrenergic receptor antagonists*. WO 0078716.

299286

1-[3-Methoxy-4-(2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-2-yl)phenyl]-1-(2,3,4,5-tetrahydro-1*H*-benzazepin-1-yl)methanone



C27 H29 N3 O2; Mol wt: 427.5451

ACTION – Vasopressin receptor antagonist ($IC_{50} = 1.7$ and 7.9 nM in V_1 and V_2 binding assays, respectively) that is expected to be of use for the treatment and/or prevention of hypertension, heart failure, renal insufficiency, edema, ascites, cerebrovascular disorders such as cerebral edema and infarction, Ménière's disease and motion sickness.

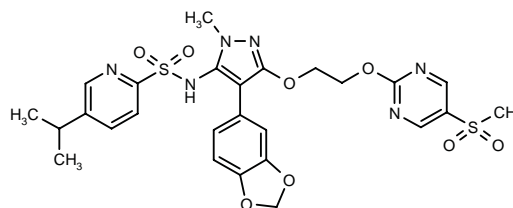
SOURCE – Fujisawa.

REFERENCES

1. Setoi, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Benzamide derivs*. WO 0100618.

299749

N-[4-(1,3-Benzodioxol-5-yl)-1-methyl-3-[2-[5-(methylsulfonyl)pyrimidin-2-yloxy]ethoxy]-1*H*-pyrazol-5-yl]-5-isopropylpyridine-2-sulfonamide



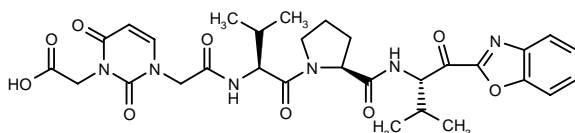
C26 H28 N6 O8 S2; Mol wt: 616.6732

BL-3730

302318

2-[N-[2-(3-Carboxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)acetyl]-L-valyl-L-prolyl-L-valyl]benzoxazole

2-[3-{2-[1(S)-[2(S)-[N-[1(S)-(Benzoxazol-2-ylcarbonyl)-2-methylpropyl]carbamoyl]-1-pyrrolidinylcarbonyl]-2-methylpropylamino]-2-oxoethyl]-2,6-dioxo-1,2,3,6-tetrahydro-1-pyrimidinyl]acetic acid



C30 H36 N6 O9; Mol wt: 624.6474

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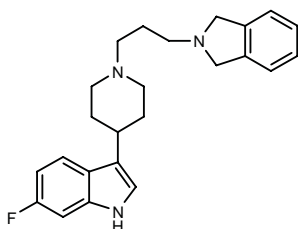
2. Inoue, Y. et al. *Design and synthesis of water-soluble novel cyclic amide-containing transition-state inhibitors of human neutrophil elastase*. 221st ACS Natl Meet (April 1–5, San Diego) 2001, Abst MEDI 242.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

299262

3-[1-[3-(2,3-Dihydro-1*H*-isoindol-2-yl)propyl]piperidin-4-yl]-6-fluoro-1*H*-indole



C24 H28 F N3; Mol wt: 377.5042

ACTION – Potent and selective α_{1B} -adrenoceptor antagonist, as demonstrated by K_i values of 0.79 and 24 nM, respectively, against [3H]-prazosin binding to α_{1B} - and α_{1A} -adrenoceptors from rat liver and rat mandibular gland. *In vivo*, compound was shown to dose-dependently (0.1–3 mg/kg/min i.v.) inhibit the phenylephrine-induced vasopressor response in rats, producing $86 \pm 2\%$ inhibition at 3 mg/kg/min. Potentially useful for the treatment of α_{1B} -adrenoceptor-related disorders, particularly hypertension. A representative compound from a series of indole derivatives.

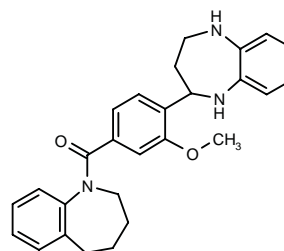
SOURCE – Toray.

REFERENCES

1. Hayasahi, R. et al. (Toray Industries, Inc.) *α_{1B} -Adrenergic receptor antagonists*. WO 0078716.

299286

1-[3-Methoxy-4-(2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-2-yl)phenyl]-1-(2,3,4,5-tetrahydro-1*H*-benzazepin-1-yl)methanone



C27 H29 N3 O2; Mol wt: 427.5451

ACTION – Vasopressin receptor antagonist ($IC_{50} = 1.7$ and 7.9 nM in V_1 and V_2 binding assays, respectively) that is expected to be of use for the treatment and/or prevention of hypertension, heart failure, renal insufficiency, edema, ascites, cerebrovascular disorders such as cerebral edema and infarction, Ménière's disease and motion sickness.

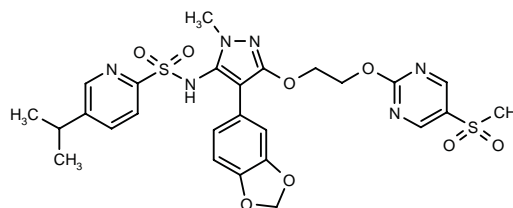
SOURCE – Fujisawa.

REFERENCES

1. Setoi, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Benzamide derivs*. WO 0100618.

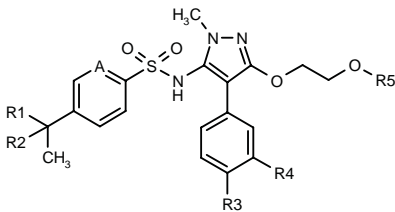
299749

N-[4-(1,3-Benzodioxol-5-yl)-1-methyl-3-[2-[5-(methylsulfonyl)pyrimidin-2-yloxy]ethoxy]-1*H*-pyrazol-5-yl]-5-isopropylpyridine-2-sulfonamide



C26 H28 N6 O8 S2; Mol wt: 616.6732

ACTION – Agent with good affinity for endothelin (ET) receptors and selectivity for ET_A over ET_B receptors, with potential for the treatment of endothelin-, particularly ET_A, mediated conditions such as restenosis, renal failure, pulmonary and systemic hypertension, as well as benign prostatic hyperplasia, male erectile dysfunction, prostate cancer, congestive heart failure, stroke, atherosclerosis, cerebral and cardiac ischemia, glaucoma, ciclosporin-induced nephrotoxicity, diabetic neuropathy, allergy and chronic obstructive pulmonary disease. Other specifically claimed compounds from this series of pyrazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
299750	H	CH2OH	-OCH2O-		5-Cl-2-pyrimidinyl	C ₂₅ H ₂₅ ClN ₆ O ₇ S
299751	Me	Me	-OCH2O-		5-Br-2-pyrimidinyl	C ₂₇ H ₂₈ BrN ₅ O ₆ S
299752	Me	CH2OH	-OCH2O-		5-Cl-2-pyrimidinyl	C ₂₇ H ₂₈ ClN ₅ O ₇ S
299753	Me	Me	-OCH2O-		5-(MeSO2)-2-pyrimidinyl	C ₂₈ H ₃₁ N ₅ O ₈ S ₂
299755	Me	CO2H	Me	H	5-Br-2-pyrimidinyl	C ₂₇ H ₂₈ BrN ₅ O ₆ S
299757	Me	CH2OH	Me	H	5-Br-2-pyrimidinyl	C ₂₇ H ₃₀ BrN ₅ O ₅ S
299758	Me	CH2OH	Me	H	Et	C ₂₈ H ₃₃ N ₃ O ₅ S
299760	Me	Me	Me	H	5-Cl-2-pyrimidinyl	C ₂₇ H ₃₀ ClN ₅ O ₄ S
299761	Me	Me	Me	H	5-(MeSO2)-2-pyrimidinyl	C ₂₈ H ₃₃ N ₅ O ₆ S ₂
299763	Me	Me	CH2OH	H	5-Br-2-pyrimidinyl	C ₂₇ H ₃₀ BrN ₅ O ₅ S
299765	Me	CH2OH	CH2OH	H	5-Br-2-pyrimidinyl	C ₂₇ H ₃₀ BrN ₅ O ₆ S

SOURCE – Pfizer.

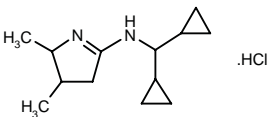
REFERENCES

1. Banks, B.J. et al. (Pfizer Inc.;Pfizer Ltd.) *Pyrazoles and their use as endothelin antagonists*. EP 1072597, JP 2001064262.

LNP-509

277195

N-(Dicyclopropylmethyl)-2,3-dimethyl-3,4-dihydro-2*H*-pyrrol-5-amine hydrochloride



C13 H22 N2 . HCl; Mol wt: 242.7917

ACTION – Antihypertensive agent, a selective ligand for the imidazoline I₁ receptor (pK_i = 6.27) relative to the I₂ receptor and α₂-adrenoceptor (pK_i < 5). Although this compound had no effect on mean arterial blood pressure (MAP) in rabbits following i.v. administration at up to 5 mg/kg, a significant reduction in MAP was seen following intracisternal injection at the dose of 1000 µg/kg, similar to that following rilmenidine (49 and 41% reduction, respectively).

SOURCES – Université Louis Pasteur, Strasbourg (FR); Servier.

REFERENCES

1. Bousquet, P. et al. (ADIR et Cie.) *Aminopyrrolidine derivs., processes for their preparation and pharmaceutical compsns. comprising them*. EP 1101756, FR 2801051.

2. Bousquet, P. et al. *Imidazoline receptors: A challenge*. Pharm Acta Helv 2000, 74(2-3): 205.

3. Bousquet, P. et al. *Participation of imidazoline receptors and α(2-)-adrenoceptors in the central hypotensive effects of imidazoline-like drugs*. Ann New York Acad Sci 1999, 881272.

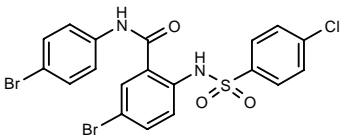
4. Bruban, V. et al. *Central hypotensive effect of LNP 509, an imidazoline compound with no detectable affinity for α₂-adrenoceptors*. J Hypertens 1999, 17(Suppl. 3): Abst P1.154.

5. Schann, S. et al. *Synthesis and biological evaluation of pyrrolinic isosteres of rilmenidine. Discovery of cis-1-trans-dicyclopropylmethyl-(4,5-dimethyl-4,5-dihydro-3*H*-pyrrol-2-yl)-amine (LNP 509), an I₁ imidazoline receptor selective ligand with hypotensive activity*. J Med Chem 2001, 44(10): 1588.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

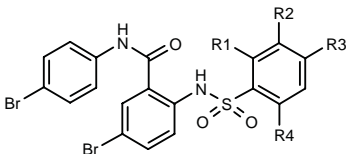
299175

5-Bromo-*N*-(4-bromophenyl)-2-(4-chlorophenylsulfonamido)benzamide



C19 H13 Br2 Cl N2 O3 S; Mol wt: 544.6497

ACTION – Macrophage scavenger receptor (MSR) antagonist that acts at an MSR group that has been recently designated SR-A. The compound is expected to be useful for the treatment of cardiovascular disorders including atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, stroke, organ transplant, organ failure, myocardial infarction and hypercholesterolemia. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	Formula
299176	H	Cl	F	H	C ₁₉ H ₁₂ Br ₂ ClFN ₂ O ₃ S
299177	Me	Cl	H	H	C ₂₀ H ₁₅ Br ₂ ClN ₂ O ₃ S
299178	Me	H	Me	Me	C ₂₂ H ₂₀ Br ₂ N ₂ O ₃ S

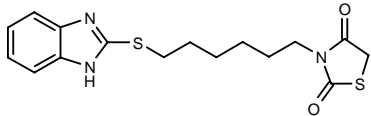
SOURCE – GlaxoSmithKline.

REFERENCES

1. Weinstock, J. et al. (SmithKline Beecham Corp.) *Macrophage scavenger receptor antagonists*. WO 0078145.

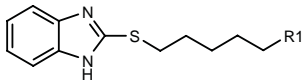
299357

3-[6-(1*H*-Benzimidazol-2-ylsulfanyl)hexyl]thiazolidine-2,4-dione



C16 H19 N3 O2 S2; Mol wt: 349.4771

ACTION – Agent for the treatment or prevention of arteriosclerosis, an inhibitor of macrophage-derived foam cell formation. *In vitro*, compound was shown to potently inhibit the formation of cholesterol esters in murine peritoneal macrophages at 5 μ M, the cholesterol ester production rate being 2.1% compared to 100% in controls. Other exemplified compounds from this series of benzimidazole derivatives include the following:



Compound	R1	Formula
299358	5-Me-2,4-dioxo-3-oxazolidinyl	C ₁₆ H ₁₉ N ₃ O ₃ S
299359	4-Ph-2,5-dioxo-1-imidazolidinyl	C ₂₁ H ₂₂ N ₄ O ₂ S
299360	5,5-(Me)2-2,4-dioxo-3-oxazolidinyl-CH2	C ₁₈ H ₂₃ N ₃ O ₃ S
299361	5,5-(Me)2-2,4-dioxo-3-oxazolidinyl-(CH2)3	C ₂₀ H ₂₇ N ₃ O ₃ S
299362	3,5-dioxo-4-morpholinyl	C ₁₆ H ₁₉ N ₃ O ₃ S
299363	4-Ph-2,5-dioxo-1-imidazolidinyl-CH2	C ₂₂ H ₂₄ N ₄ O ₂ S

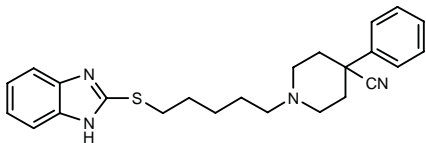
SOURCE – Fuji Photo Film.

REFERENCES

1. Aoki, K. et al. (Fuji Photo Film Co., Ltd.) *Benzimidazole cpds. and drugs containing the same*. WO 0100613.

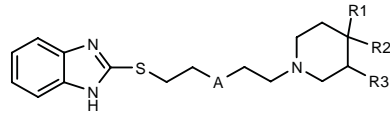
299364

1-[5-(1*H*-Benzimidazol-2-ylsulfanyl)pentyl]-4-phenyl-piperidine-4-carbonitrile

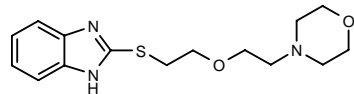


C24 H28 N4 S; Mol wt: 404.5792

ACTION – Agent for the treatment or prevention of arteriosclerosis, an inhibitor of macrophage-derived foam cell formation. *In vitro*, compound was shown to potently inhibit the formation of cholesterol esters in murine peritoneal macrophages at 5 μ M, the cholesterol ester production rate being 4.1% compared to 100% in controls. Other exemplified compounds from this series of benzimidazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
299365	H	Me	H	-CH2-	C ₁₈ H ₂₇ N ₃ S
299366	H	H	CH2OH	-CH2-	C ₁₈ H ₂₇ N ₃ OS
299367	Ph	Ac	H	-CH2-	C ₂₅ H ₃₁ N ₃ OS
299368	OH	Ph	H	-CH2-	C ₂₃ H ₂₉ N ₃ OS
299369	Ph	CN	H	-(CH2)4-	C ₂₇ H ₃₄ N ₄ S



299371: C15 H21 N3 O2 S

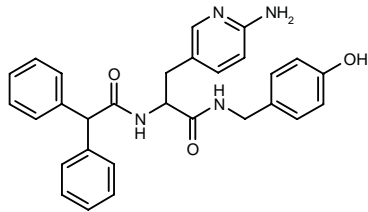
SOURCE – Fuji Photo Film.

REFERENCES

1. Aoki, K. et al. (Fuji Photo Film Co., Ltd.) *Benzimidazole cpds. and drugs containing the same*. WO 0100588.

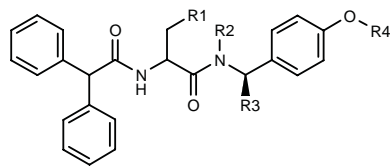
299949

3-(6-Aminopyridin-3-yl)-2-(diphenylacetamido)-*N*-(4-hydroxybenzyl)propionamide



C29 H28 N4 O3; Mol wt: 480.5652

ACTION – Neuropeptide Y (NPY) antagonist with affinity for Y₁ receptors (IC₅₀ < 5 μ M). Potential uses of this compound include cardiovascular disorders such as angina pectoris, myocardial infarction and syndrome X, obesity and other NPY-mediated diseases, particularly vasoconstriction. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
299950	6-NH2-3-Pyr	H	H	Me	C ₃₀ H ₃₀ N ₄ O ₃
299951	2-NH2-4-Pyr-CH2	H	H	H	C ₃₀ H ₃₀ N ₄ O ₃
299952	2-NH2-4-Pyr-CH2	H	H	Me	C ₃₁ H ₃₂ N ₄ O ₃
299953	6-NH2-3-Pyr-CH2	H	H	Me	C ₃₁ H ₃₂ N ₄ O ₃
299954	6-NH2-3-Pyr	Me	H	Me	C ₃₁ H ₃₂ N ₄ O ₃
299955	2-NH2-4-Pyr-CH2	H	Me	H	C ₃₁ H ₃₂ N ₄ O ₃
299956	2-NH2-4-Pyr-CH2	Me	H	H	C ₃₁ H ₃₃ ClN ₄ O ₃
299957	6-NH2-3-Pyr	H	Me	H	C ₃₀ H ₃₀ N ₄ O ₃

SOURCE – AstraZeneca.

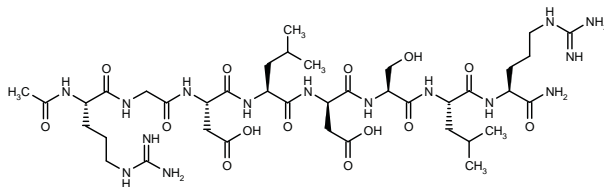
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1. Antonsson, T. et al. (AstraZeneca AB) *New NPY antagonists*. WO 0102364.

EMD-272974

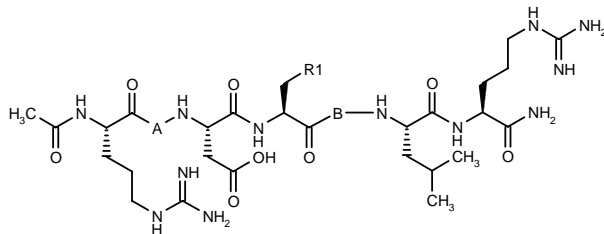
299276

N-Acetyl-L-arginyl-glycyl-L-aspartyl-L-leucyl-D-aspartyl-L-seryl-L-leucyl-L-argininamide



C39 H69 N15 O14; Mol wt: 972.0651

ACTION – Integrin $\alpha_v\beta_6$ inhibitor with an IC₅₀ of 11.25 nM when tested for inhibition of the binding of fibrinogen to the human $\alpha_v\beta_6$ receptor. This compound is specifically claimed for the treatment of thrombosis, myocardial infarction, coronary artery disease, arteriosclerosis, tumors, osteoporosis, fibrosis, inflammation, infections, psoriasis and wound-healing disorders. Other exemplified peptides are:



Compound	R1	A	B	Formula
EMD-271297 [299277]	i-Pr	-Gly-	-L-Asp-L-Ser-	C ₃₉ H ₆₉ N ₁₅ O ₁₄
EMD-271288 [299279]	i-Pr	-L-Thr-	-D-Asp-L-Ser-	C ₄₁ H ₇₃ N ₁₅ O ₁₅
EMD-271309 [299280]	i-Pr	-L-Thr-	-D-Ala-L-Ser-	C ₄₀ H ₇₃ N ₁₅ O ₁₃
EMD-249385 [299281]	Pr	-L-Thr-	-D-Asp-L-Ser-	C ₄₁ H ₇₃ N ₁₅ O ₁₅
EMD-271314 [299283]	i-Pr	-L-Thr-	-D-Asp-D-Ser-	C ₄₁ H ₇₃ N ₁₅ O ₁₅

SOURCE – Merck KGaA.

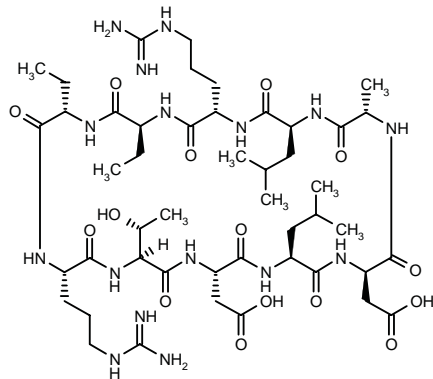
REFERENCES

1. Jonczyk, A. et al. (Merck Patent GmbH) *Inhibitors of the integrin $\alpha_v\beta_6$* . DE 19929410, WO 0100660.

EMD-273040

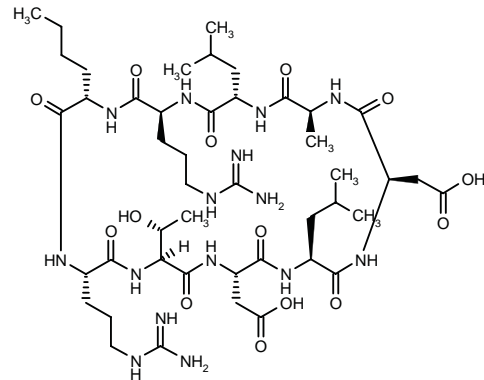
300350

Cyclo[L-arginyl-L-threonyl-L-aspartyl-L-leucyl-D-aspartyl-L-alanyl-L-leucyl-L-arginyl-L-(2-aminobutyryl)-L-(2-aminobutyryl)]

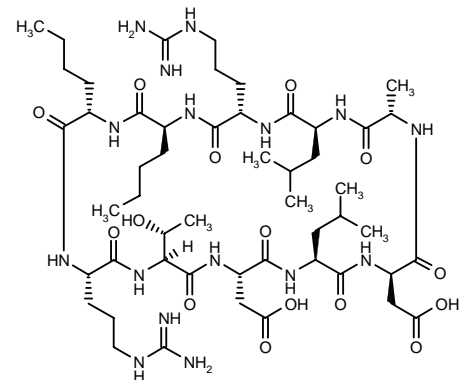


C47 H82 N16 O15; Mol wt: 1111.2620

ACTION – Cyclic peptide that inhibits the $\alpha_v\beta_6$ integrin receptor (IC₅₀ = 1.05 nM for inhibition of the binding of fibrinogen to the human $\alpha_v\beta_6$ receptor), potentially useful for the treatment of thrombosis, myocardial infarction, coronary artery disease, arteriosclerosis, tumors, osteoporosis, fibrosis, inflammation, infections, psoriasis and wound-healing disorders. Other exemplified peptides are:



EMD-273028 [300351]: C45 H79 N15 O14



EMD-273038 [300352]: C51 H90 N16 O15

SOURCE – Merck KGaA.

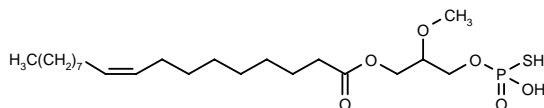
REFERENCES

1. Jonczyk, A. et al. (Merck Patent GmbH) *Cyclic peptide derivs. as inhibitors of integrin $\alpha v \beta 6$* . DE 19933173, WO 0105810.

LXR-1035

270603

9(*Z*)-Octadecenoic acid 2-methoxy-3-(thiophosphonoxy)propyl ester



C22 H43 O6 P S; Mol wt: 466.6157

ACTION – Synthetic phosphorothioate analogue of oleoyl lysophosphatidic acid proven to significantly inhibit leukocyte–endothelial cell interactions in rat mesenteric microvasculature during acute inflammatory events. These effects were mediated via inhibition of P-selectin in endothelial cells and suppression of CD18 in circulating neutrophils. Moreover, compound was able to prevent all steps of apoptotic cell death including caspase 3 activation, DNA degradation, cell permeabilization and detachment induced by glucose deprivation and hypoxia/normoxia in rat neonatal cardiomyocytes. *In vivo* studies in a model of myocardial infarction and ischemia–reperfusion injury in rats showed that compound (75 and 750 nmol/kg/h) significantly reduced the percent myocardial infarct per heart as well as the percent infarct area at risk. Potentially useful as adjunctive therapy for the prevention of ischemia–reperfusion injury in myocardial infarction.

SOURCE – LXR Biotechnology.

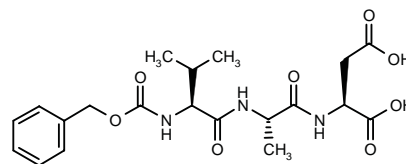
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1. Bathurst, I.C. et al. (LXR Biotechnology Inc.) *Compsns. containing lysophosphatidic acids which inhibit apoptosis and uses thereof*. WO 9841213.
2. Goddard, J.G. et al. (LXR Biotechnology Inc.; Evotec Biosystems AG) *Compsns. containing lysophosphatidic acids which inhibit apoptosis and uses thereof*. WO 9947101.
3. Scalia, R. et al. *A novel lysophosphatidic acid analog, LXR-1035, inhibits leukocyte-endothelium interaction via inhibition of cell adhesion molecules*. J Leukocyte Biol 2000, 67(1): 26.
4. Singh, M. et al. *A novel analog of lysophosphatidic acid protects the retina after brief periods of ischemia*. Soc Neurosci Abst 1999, 25(Part 2): Abst 636.1.
5. Zellner, C. et al. *LXR1035 a novel lysophosphatic acid analog attenuates ischemia-reperfusion injury*. J Am Coll Cardiol 2001, 37(2, Suppl. A): 377A.
6. *LXR initiates preclinical development of second-generation analogue of Elirex*. DailyDrugNews.com (Daily Essentials) 1998, Dec 4.

Z-VAD

300866

N-(Benzyloxycarbonyl)-L-valyl-L-alanyl-L-aspartic acid



C20 H27 N3 O8; Mol wt: 437.4463

ACTION – Caspase inhibitor found to protect arterial medial smooth muscle cells from balloon injury-mediated apoptosis in rabbits. Compound delivered locally at doses of 4.5 or 45 μ g/animal to rabbits undergoing bilateral iliac artery angioplasty significantly decreased the apoptotic index (33 and 45% reduction, respectively, compared to placebo). Potentially useful for the prevention of restenosis.

SOURCE – Northwestern University, Evanston, IL (US).

REFERENCES

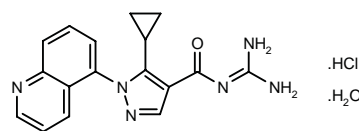
1. Baker, M.S. et al. *Caspase inhibition in murine islets blocks nitric oxide dependent cytokine-induced apoptosis without preserving islet function*. Am J Transplant 2001, 1(Suppl. 1): Abst 1249.
2. Beohar, N. et al. *Inhibition of balloon injury mediated apoptosis with local delivery of a caspase inhibitor*. J Am Coll Cardiol 2001, 37(2, Suppl. A): 44A.
3. Sané, A.-T. and Bertrand, R. *Distinct steps in DNA fragmentation pathway during camptothecin-induced apoptosis involved caspase-, benzyloxycarbonyl- and N-tosyl-L-phenylalanylchloromethyl ketone-sensitive activities*. Cancer Res 1998, 58(14): 3066.

ZONIPORIDE HYDROCHLORIDE

295863

N'-[5-Cyclopropyl-1-(5-quinolyl)-1*H*-pyrazol-4-yl]carbonyl]guanidine hydrochloride monohydrate

CP-597396



C17 H16 N6 O . HCl . H2O; Mol wt: 374.8301

ACTION – Potent and selective inhibitor of Na⁺/H⁺ exchanger isoform 1 (NHE-1) with an IC₅₀ of 59 nM for inhibition of human NHE-1 compared to an IC₅₀ of 12,000 nM for inhibition of human NHE-2 and > 500,000 nM for inhibition of rat NHE-3. In addition to its potency, compound exhibited high water solubility and a pharmacokinetic profile suitable for parenteral administration. It potently inhibited human platelet swelling *ex vivo* (IC₅₀ = 54 nM) and reduced ischemic myocardial injury in isolated rabbit hearts (EC₅₀ = 0.25 nM), being 2.5-20-fold more potent than either eniporide or cariporide (EC₅₀ = 0.69 and 5.11 nM, respectively). In a rabbit model of ischemia/reperfusion-induced myocardial ischemic injury, compound dose-dependently reduced infarct size (ED₅₀ = 0.45 mg/kg/h) and inhibited NHE-1-mediated platelet swelling (93% at 4 mg/kg/h), without altering hemodynamics.

SOURCE – Pfizer.

REFERENCES

1. Hamanaka, E.S. et al. (Pfizer Products Inc.) *N-[(Substd. five-membered di- or triaza diunsaturated ring)carbonyl] guanidine derivs. for the treatment of ischemia.* EP 1056729, WO 9943663.

2. Flynn, D.M. et al. *A novel NHE-1 inhibitor reduces myocardial stunning in conscious primates.* Circulation 2000, 102(18, Suppl.): Abst 665.

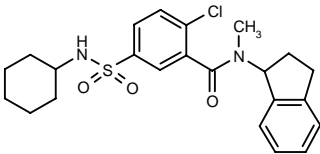
3. Guzman-Perez, A. et al. *Discovery of zoniporide: A potent and selective sodium-hydrogen exchanger type 1 (NHE-1) inhibitor with high aqueous solubility.* Bioorg Med Chem Lett 2001, 11(6): 803.

4. Knight, D.R. et al. *A novel sodium-hydrogen exchanger isoform-1 inhibitor, zoniporide, reduces ischemic myocardial injury in vitro and in vivo.* J Pharmacol Exp Ther 2001, 297(1): 254.

ANTIARRHYTHMIC DRUGS

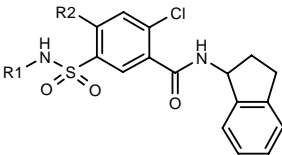
299435

2-Chloro-5-(cyclohexylsulfamoyl)-*N*-(2,3-dihydro-1 *H*-inden-1-yl)-*N*-methylbenzamide



C23 H27 Cl N2 O3 S; Mol wt: 446.9963

ACTION – A selective inhibitor of Kv1.5 potassium channels (IC₅₀ = 2.2 μM for inhibition of human Kv1.5 channels expressed in *Xenopus* oocytes), potentially useful as an antiarrhythmic agent, particularly for the treatment or prevention of atrial arrhythmias such as atrial fibrillation or atrial flutter. Other exemplified compounds from this series of indanyl-substituted benzamides include the following:



Compound	R1	R2	Isomer	Formula
299436	i-BuCH2	Cl		C ₂₁ H ₂₄ Cl ₂ N ₂ O ₃ S
299437	cyclohexyl	Cl		C ₂₂ H ₂₄ Cl ₂ N ₂ O ₃ S
299438	i-BuCH2	Cl	R	C ₂₁ H ₂₄ Cl ₂ N ₂ O ₃ S
299439	i-BuCH2	Cl	S	C ₂₁ H ₂₄ Cl ₂ N ₂ O ₃ S
299440	4-MeO-Ph	F		C ₂₃ H ₂₀ ClFN ₂ O ₄ S

SOURCE – Aventis Pharma.

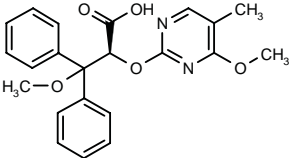
REFERENCES

1. Brendel, J. et al. (Aventis Pharma Deutschland GmbH) *Indanyl-substd. benzole carbonamide, method for the production of the same, use thereof as a medicament and pharmaceutical preparations containing the same.* DE 19929076, WO 0100573.

HEART FAILURE THERAPY

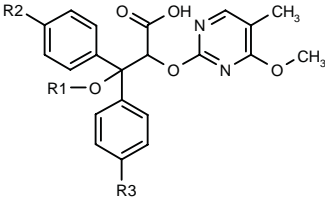
300288

3-Methoxy-2(*S*)-(4-methoxy-5-methylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid



C22 H22 N2 O5; Mol wt: 394.4248

ACTION – Agent for the treatment of chronic heart failure, restenosis, hypertension, pulmonary hypertension, acute and chronic renal disorders, cerebral ischemia, asthma, benign prostatic hyperplasia, prostate cancer and acute pancreatitis with endothelin receptor-antagonist activity. In a binding assay, compound gave a K_i value of 0.6 nM against human ET_A receptors cloned in CHO cells. Other exemplified compounds from this series of carboxylic acid derivatives with a 5,6-substituted pyrimidine ring include the following:



Compound	R1	R2=R3	Formula
300289	Et	H	C ₂₃ H ₂₄ N ₂ O ₅
300290	i-Pr	H	C ₂₄ H ₂₆ N ₂ O ₅
300291	CH2Ph	H	C ₂₈ H ₂₆ N ₂ O ₅
300292	Me	F	C ₂₂ H ₂₀ F ₂ N ₂ O ₅
300293	3,4-(Me)2-PhCH2	H	C ₃₀ H ₃₀ N ₂ O ₅

SOURCE – BASF.

REFERENCES

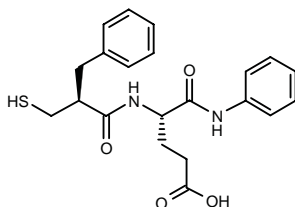
1. Amberg, W. and Ketttschau, G. (BASF AG) *Novel carboxylic acid derivs. with 5,6 substd. pyrimidine ring, the production and utilization thereof as endothelin receptor antagonists.* DE 19933164, WO 0105771.

ONO-BB-039-02

302101

4(*S*)-[3-Phenyl-2(*S*)-(sulfanylmethyl)propionamido]-5-oxo-5-(phenylamino)pentanoic acid

*N*²-[2(*S*)-Benzyl-3-sulfanylpropionyl]-L-glutamic acid 1-phenylamide



C21 H24 N2 O4 S; Mol wt: 400.4966

ACTION – Neutral endopeptidase (NEP) inhibitor proven to slightly enhance the endogenous atrial natriuretic peptide (NAP)-induced decrease in collagen synthesis by cultured neonatal rat cardiac fibroblasts. Potentially useful for the treatment of heart failure.

SOURCE – Ono.

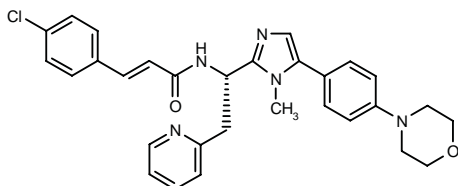
REFERENCES

1. Kawamura, M. et al. (Ono Pharmaceutical Co., Ltd.) *Novel amino acid derivs.* EP 0341081, JP 1990209861, JP 1994179649, US 5017589, US 5202340, US 5317021.
2. Maki, T. et al. *Effect of neutral endopeptidase inhibitor on endogenous atrial natriuretic peptide as a paraacrine factor in cultured cardiac fibroblasts.* Br J Pharmacol 2000, 131(6): 1204.
3. Senokuchi, K. et al. *New orally active enkephalinase inhibitors: Their synthesis, biological activity, and analgesic properties.* Bioorg Med Chem 1998, 6(4): 441.
4. Toshiyuki, M. et al. *Neutral endopeptidase inhibition enhances endogenous ANP-induced suppression of collagen synthesis in cultured cardiac fibroblasts.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-59.

MISCELLANEOUS CARDIOVASCULAR DRUGS

299672

3-(4-Chlorophenyl)-*N*-[1(*S*)-[1-methyl-5-[4-(4-morpholinyl)phenyl]-1*H*-imidazol-2-yl]-2-(2-pyridinyl)ethyl]-2(*E*)-propenamide



C30 H30 Cl N5 O2; Mol wt: 528.0530

ACTION – An inhibitor of the production of nitric oxide (NO; 100% inhibition against lipopolysaccharide- and interferon gamma-stimulated NO production in murine macrophage RAW264.7 cells at 1 μM) that is believed to act either by inhibition of nitric oxide synthase (NOS) or by inhibition of NOS production. Potentially useful in the treatment or prevention of NO-mediated disorders such as cardiovascular, respiratory, endocrine, renal, gastrointestinal, autoimmune, CNS and dermal diseases, pancreatitis, bone or joint disorders, cancer, transplant rejection, septic shock and sexual dysfunction. A representative compound from a series of *N*-imidazolymethyl carboxamides.

SOURCE – Fujisawa.

REFERENCES

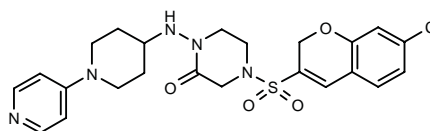
1. Shima, I. et al. (Fujisawa Pharmaceutical Co., Ltd.) *N-Imidazolymethyl carboxamides as nitric oxide production inhibitors.* WO 0102387.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

299263

4-(7-Chloro-2*H*-1-benzopyran-3-ylsulfonyl)-1-[1-(4-pyridinyl)piperidin-4-ylamino]piperazin-2-one



C23 H26 Cl N5 O4 S; Mol wt: 504.0084

ACTION – Anticoagulant and antithrombotic agent, a human factor Xa inhibitor (IC₅₀ = 0.0058 μM). A representative compound from a series of acylhydrazine derivatives.

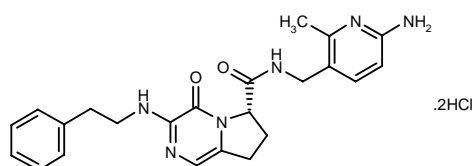
SOURCE – Takeda.

REFERENCES

1. Itoh, F. et al. (Takeda Chemical Industries, Ltd.) *Acylhydrazine derivs., process for preparing the same and use thereof.* WO 0078747.

299313

N-(6-Amino-2-methylpyridin-3-ylmethyl)-4-oxo-3-(2-phenylethylamino)-4,6,7,8-tetrahydropyrrolo[1,2-*a*]-pyrazine-6(*S*)-carboxamide dihydrochloride



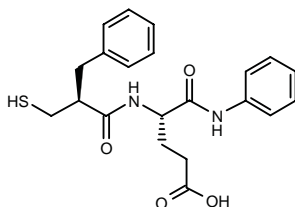
C23 H26 N6 O2 . 2HCl; Mol wt: 491.4202

ONO-BB-039-02

302101

4(*S*)-[3-Phenyl-2(*S*)-(sulfanylmethyl)propionamido]-5-oxo-5-(phenylamino)pentanoic acid

*N*²-[2(*S*)-Benzyl-3-sulfanylpropionyl]-L-glutamic acid 1-phenylamide



C21 H24 N2 O4 S; Mol wt: 400.4966

ACTION – Neutral endopeptidase (NEP) inhibitor proven to slightly enhance the endogenous atrial natriuretic peptide (NAP)-induced decrease in collagen synthesis by cultured neonatal rat cardiac fibroblasts. Potentially useful for the treatment of heart failure.

SOURCE – Ono.

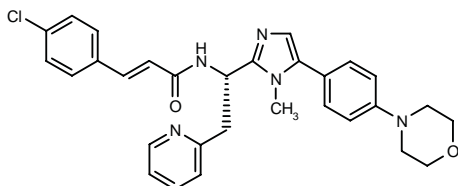
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MISCELLANEOUS CARDIOVASCULAR DRUGS

299672

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C30 H30 Cl N5 O2; Mol wt: 528.0530

ACTION – An inhibitor of the production of nitric oxide (NO; 100% inhibition against lipopolysaccharide- and interferon gamma-stimulated NO production in murine macrophage RAW264.7 cells at 1 μM) that is believed to act either by inhibition of nitric oxide synthase (NOS) or by inhibition of NOS production. Potentially useful in the treatment or prevention of NO-mediated disorders such as cardiovascular, respiratory, endocrine, renal, gastrointestinal, autoimmune, CNS and dermal diseases, pancreatitis, bone or joint disorders, cancer, transplant rejection, septic shock and sexual dysfunction. A representative compound from a series of *N*-imidazolymethyl carboxamides.

SOURCE – Fujisawa.

REFERENCES

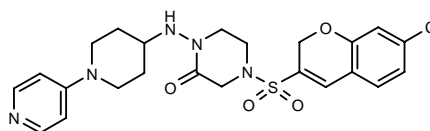
1. Shima, I. et al. (Fujisawa Pharmaceutical Co., Ltd.) *N-Imidazolymethyl carboxamides as nitric oxide production inhibitors.* WO 0102387.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

299263

4-(7-Chloro-2*H*-1-benzopyran-3-ylsulfonyl)-1-[1-(4-pyridinyl)piperidin-4-ylamino]piperazin-2-one



C23 H26 Cl N5 O4 S; Mol wt: 504.0084

ACTION – Anticoagulant and antithrombotic agent, a human factor Xa inhibitor (IC₅₀ = 0.0058 μM). A representative compound from a series of acylhydrazine derivatives.

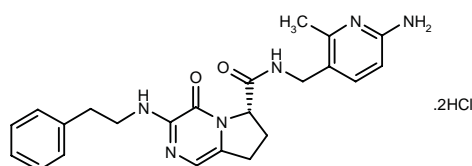
SOURCE – Takeda.

REFERENCES

1. Itoh, F. et al. (Takeda Chemical Industries, Ltd.) *Acylhydrazine derivs., process for preparing the same and use thereof.* WO 0078747.

299313

N-(6-Amino-2-methylpyridin-3-ylmethyl)-4-oxo-3-(2-phenylethylamino)-4,6,7,8-tetrahydropyrrolo[1,2-*a*]-pyrazine-6(*S*)-carboxamide dihydrochloride



C23 H26 N6 O2 . 2HCl; Mol wt: 491.4202

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of thrombin, as demonstrated *in vitro* by IC₅₀ values of 34, > 33,000, > 33,000 and > 33,000 nM, respectively, against human thrombin, plasmin, tPA and uPA. In addition, compound produced marked prolongation of the thrombin time (TT) and activated cephalin time (ACT) both *in vitro* in human plasma, where it doubled them at 3 and 9.1 µM, respectively, and *in vivo* in dogs, where it increased TT by 3.6-fold and ACT by 1.6-fold when given at 3 mg/kg p.o. A specifically claimed compound from a series of bicyclic derivatives of 4-aminopyrazinones.

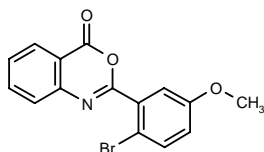
SOURCE – ADIR.

REFERENCES

1. de Nanteuil, G. et al. (ADIR et Cie.) *Bicyclic derivs. of amino-pyrazinones, process of preparation and pharmaceutical compns. comprising them*. EP 1069132, FR 2795072, JP 2001026592.

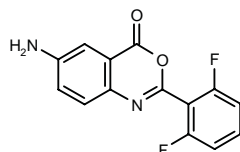
299739

2-(2-Bromo-5-methoxyphenyl)-4*H*-3,1-benzoxazin-4-one



C15 H10 Br N O3; Mol wt: 332.1520

ACTION – Anticoagulant that acts by inhibiting factor VIIa/tissue factor (FVIIa/TF) activity. *In vitro*, compound was shown to inhibit FVIIa/TF-catalyzed activation of factor X (IC₅₀ = 1.1 µM) as well as FVIIa/TF-induced clotting of human plasma, increasing clotting time by > 30-fold at a concentration of 0.33 mM. Another exemplified benzoxazin derivative is:



299741: C14 H8 F2 N2 O2

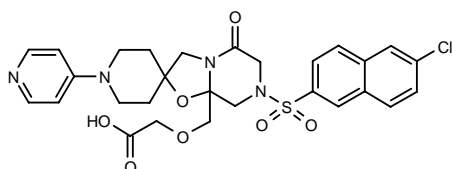
SOURCE – Novo Nordisk.

REFERENCES

1. Persson, E. et al. (Novo Nordisk A/S) *Heterocyclic cpds. regulating clotting*. US 6180625.

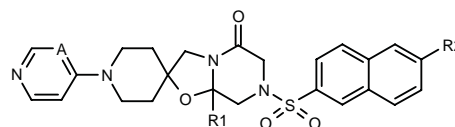
299832

2-[7-(6-Chloronaphthalen-2-ylsulfonyl)-5-oxo-1'-(4-pyridyl)spiro[2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]-pyrazin-2,4'-piperidin]-8a-ylmethoxy]acetic acid

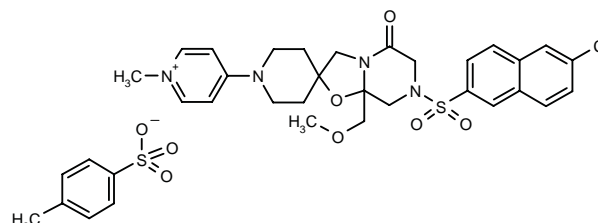


C28 H29 Cl N4 O7 S; Mol wt: 601.0771

ACTION – Anticoagulant that inhibits the blood coagulation factor Xa (IC₅₀ = 0.0029 µM). The compound exhibited anticoagulant activity *in vitro*, doubling the activated partial thromboplastin time (APTT) in human plasma at a concentration of 0.43 µM. Other tricyclic compounds are:



Compound	R1	R2	A	Formula
299834	CH2OMe	Cl	CH	C ₂₇ H ₂₉ ClN ₄ O ₅ S
299835	CH2OMe	H	CH	C ₂₇ H ₃₀ N ₄ O ₅ S
299836	H	Cl	CH	C ₂₆ H ₂₅ ClN ₄ O ₄ S
299837	H	Cl	N	C ₂₄ H ₂₄ ClN ₅ O ₄ S
299839	CO2Et	Cl	CH	C ₂₈ H ₂₉ ClN ₄ O ₆ S
299840	i-PrOCO	Cl	CH	C ₂₉ H ₃₁ ClN ₄ O ₆ S
299841	CO2CH2CH2OMe	Cl	CH	C ₂₉ H ₃₁ ClN ₄ O ₇ S
299842	CO ₂ ⁻ NH ₄ ⁺	Cl	CH	C ₂₆ H ₂₈ ClN ₅ O ₆ S
299843	CH2NH2	Cl	CH	C ₂₆ H ₂₈ ClN ₅ O ₄ S
299844	CH2NHCO2Et	Cl	CH	C ₂₉ H ₃₂ ClN ₅ O ₆ S
299845	4-morpholinyl-CH2	Cl	CH	C ₃₀ H ₃₄ ClN ₆ O ₅ S
299846	Me	Cl	CH	C ₂₆ H ₂₇ ClN ₄ O ₄ S



299838: C28 H32 Cl N4 O5 S . C7 H7 O3 S

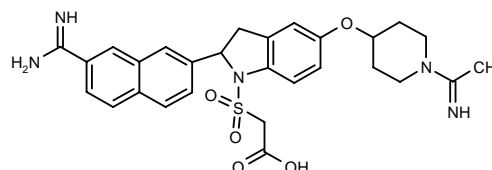
SOURCE – Mochida.

REFERENCES

1. Nishida, H. et al. (Mochida Pharmaceutical Co., Ltd.) *Tricyclic cpds. having spiro union*. WO 0102397.

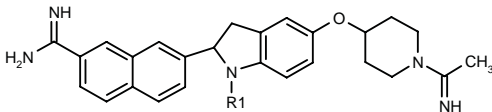
300022

2-[2-(7-Amidinonaphthalen-2-yl)-5-[1-(ethanimidoyl)-piperidin-4-yloxy]-2,3-dihydro-1*H*-indol-1-ylsulfonyl]acetic acid



C28 H31 N5 O5 S; Mol wt: 549.6489

ACTION – Anticoagulant, a factor Xa inhibitor, as demonstrated by an IC₅₀ of 2.4 ng/ml against human factor Xa. Other exemplified compounds within this series of indoline and tetrahydroquinoline derivatives are:



Compound	R1	Formula
300023	SO2Me	C ₂₇ H ₃₁ N ₅ O ₃ S
300024	SO2Bu	C ₃₀ H ₃₇ N ₅ O ₃ S
300025	SO2CH2CO2Et	C ₃₀ H ₃₅ N ₅ O ₅ S
300026	Ac	C ₂₈ H ₃₁ N ₅ O ₂
300027	COCH2OH	C ₂₈ H ₃₁ N ₅ O ₃

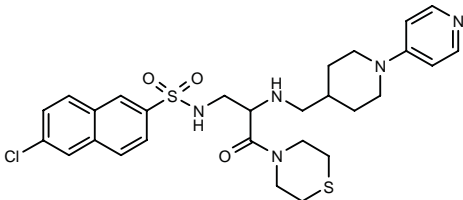
SOURCE – Sankyo.

REFERENCES

1. Fujimoto, K. et al. (Sankyo Co., Ltd.) *Indoline or tetrahydroquinoline derivs.* JP 2001072662, WO 0102356.

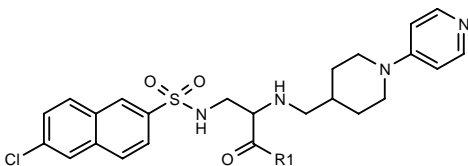
300155

6-Chloro-*N*-[3-oxo-2-[1-(4-pyridinyl)piperidin-4-yl-methylamino]-3-(4-thiomorpholinyl)propyl]naphthalene-2-sulfonamide



C28 H34 Cl N5 O3 S2; Mol wt: 588.1936

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of human factor Xa (IC₅₀ = 0.050 μM). Compound was shown to double prothrombin time (PT) in rat plasma at 0.42 μM and is reported to prolong activated partial thromboplastin time (APTT) in human plasma. Other compounds from this series of aminoalkylsulfonamide derivatives include the following:



Compound	R1	Formula
300157	OEt	C ₂₈ H ₃₁ ClN ₅ O ₄ S
300158	1-Pip	C ₂₉ H ₃₆ ClN ₅ O ₃ S
300159	4-morpholinyl	C ₂₈ H ₃₄ ClN ₅ O ₄ S
300160	1,1-dioxo-4-thiomorpholinyl	C ₂₈ H ₃₄ ClN ₅ O ₅ S ₂

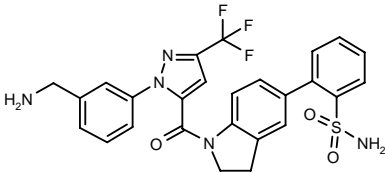
SOURCE – Mochida.

REFERENCES

1. Nishida, H. and Shimada, H. (Mochida Pharmaceutical Co., Ltd.) *Amino alkyl sulfonamide derivs.* JP 2001011071.

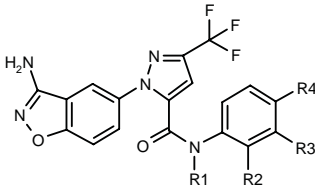
300430

2-[1-[1-(3-Aminomethylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-ylcarbonyl]-2,3-dihydro-1*H*-indol-5-yl]benzene-sulfonamide

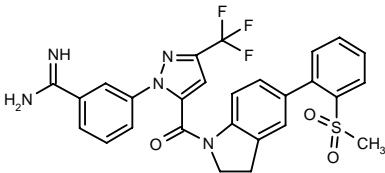


C26 H22 F3 N5 O3 S; Mol wt: 541.5518

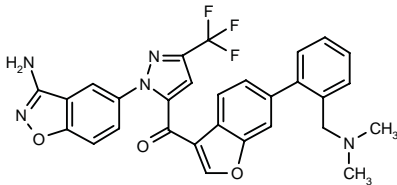
ACTION – Anticoagulant and antithrombotic agent, an inhibitor of trypsin-like serine proteases, especially factor Xa. Other specifically claimed compounds from this series of nitrogen-containing heterobicycles include the following:



Compound	R1,R2	R3	R4	Formula
300431	-(CH2)2-	H	2-(MeSO2)-Ph	C ₂₇ H ₂₀ F ₃ N ₅ O ₄ S
300432	-(CH2)4-	H	2-(NH2SO2)-Ph	C ₂₈ H ₂₃ F ₃ N ₅ O ₄ S
300433	-CH=CH-	2-(MeSO2)-Ph	H	C ₂₇ H ₁₈ F ₃ N ₅ O ₄ S
300434	-CH2CH2NH-	H	2-(NH2SO2)-Ph	C ₂₆ H ₂₀ F ₃ N ₇ O ₄ S
300435	-(CH2)3NH-	H	2-(NH2SO2)-Ph	C ₂₇ H ₂₂ F ₃ N ₇ O ₄ S
300437	-CH2CH2OCH2-	H	2-(NH2SO2)-Ph	C ₂₇ H ₂₁ F ₃ N ₆ O ₅ S



300436: C27 H22 F3 N5 O3 S



300438: C29 H22 F3 N5 O3

300438

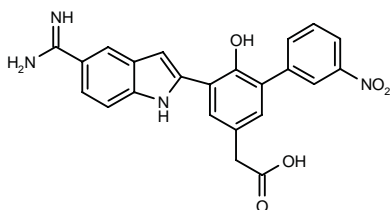
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Jacobson, I.C. and Quan, M.L. (DuPont Pharmaceuticals Co.) *Nitrogen containing heterobicycles as factor Xa inhibitors.* WO 0105784.

301921

2-[5-(5-Amidino-1*H*-indol-2-yl)-6-hydroxy-3'-nitrophenyl]-3-yl]acetic acid



C23 H18 N4 O5; Mol wt: 430.4182

ACTION – Anticoagulant, a potent factor VIIa/tissue factor (TF) complex inhibitor ($K_i = 3$ nM) with high selectivity over thrombin, plasmin, trypsin and urokinase-type plasminogen activator ($K_i = 960, 90, 160$ and 64 nM, respectively). It was able to double the prothrombin time at 1.7 μ M.

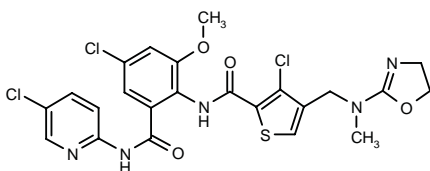
SOURCE – Axys Pharmaceuticals.

REFERENCES

1. Young, W.B. et al. *Optimization of a screening lead for factor VIIIA/TF*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 48.

301965

3-Chloro-*N*-[4-chloro-2-(5-chloropyridin-2-ylcarbamoyl)-6-methoxyphenyl]-4-[[*N*-(4,5-dihydro-1,3-oxazol-2-yl)-*N*-methylamino]methyl]-2-thiophenecarboxamide



C23 H20 Cl3 N5 O4 S; Mol wt: 568.8670

ACTION – Potent and selective factor Xa inhibitor ($K_i = 0.007$ nM) proven to produce a 2-fold prolongation of human prothrombin time at 0.35 μ M. Compound exhibited a favorable oral pharmacokinetic profile in dogs, where peak plasma levels of $3-5$ μ M were reached at 4 h after oral administration (10 mg/kg) and remained above 1 μ M at 6 h; oral bioavailability was about 40% and the *ex vivo* prothrombin time was prolonged up to 6-fold. In the rat vena cava stasis model of thrombosis, compound reduced thrombus weight with an ED_{50} of about 0.4 mg/kg i.v.

SOURCE – Berlex.

REFERENCES

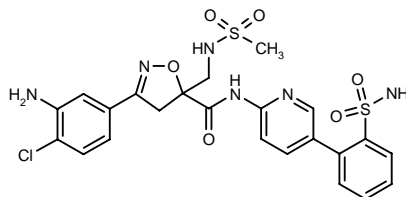
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2. Ye, B. et al. *Design, synthesis, and biological activity of novel non-amidine factor Xa inhibitors*. 4: *Optimization of hydrophilic substituents for potency and oral availability*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 128.

ST-368

301978

(-)-3-(3-Amino-4-chlorophenyl)-5-(methylsulfonyl-methyl)-*N*-[5-(2-sulfamoylphenyl)pyridin-2-yl]-4,5-dihydroisoxazole-5-carboxamide



C23 H23 Cl N6 O6 S2; Mol wt: 579.0557

ACTION – Coagulation factor Xa inhibitor ($K_i = 1.5$ nM), a nonbenzamidine isoxazoline derivative with high selectivity over other serine protease including thrombin and trypsin ($K_i = 800$ and > 8000 nM, respectively). When compared with the benzamidine inhibitor SM-084, compound exhibited slightly lower potency ($K_i = 0.11$ nM) but an improved pharmacokinetic profile, with reduced clearance and a longer half-life ($t_{1/2} = 7.25$ and 1.1 h, respectively). Potentially useful for the treatment of arterial and venous thrombosis.

SOURCE – DuPont Pharmaceuticals.

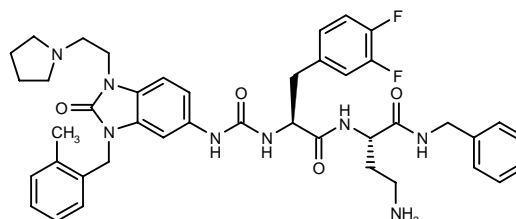
REFERENCES

1. Quan, M.L. et al. *Nonbenzamidine isoxazolin derivatives as factor Xa inhibitors*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 52.

ANTIPLATELET THERAPY

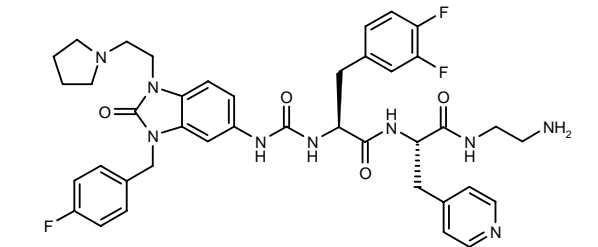
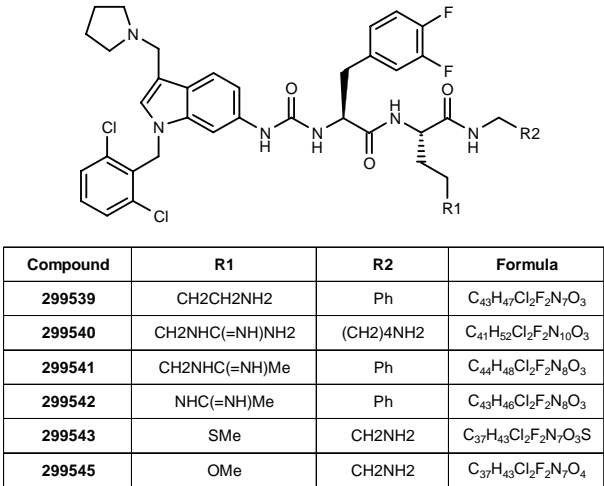
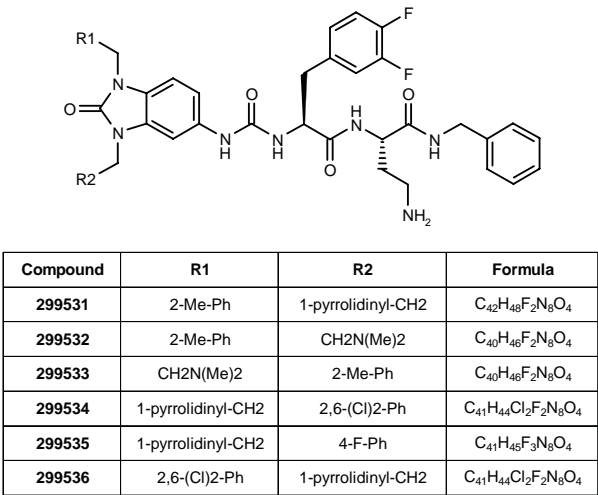
299530

*N*¹-[3-Amino-1-(*S*)-(benzylcarbamoyl)propyl]-3,4-difluoro-*N*^α-[*N*-[3-(2-methylbenzyl)-2-oxo-1-[2-(1-pyrrolidinyl)ethyl]-2,3-dihydro-1*H*-benzimidazol-5-yl]carbamoyl]-*L*-phenylalaninamide



C42 H48 F2 N8 O4; Mol wt: 766.8892

ACTION – Thrombin receptor (PAR-1) antagonist, potentially useful in the treatment of thrombosis, restenosis, hypertension, heart failure, arrhythmia, myocardial infarction, glomerulonephritis, inflammation, stroke, atherosclerosis, ischemic conditions, neurodegenerative disorders, angiogenic disorders and cancer. *In vitro*, compound gave IC_{50} values of 0.4 and 0.28 μ M in a PAR-1 binding assay and a thrombin-induced gel-filtered platelet aggregation assay, respectively. Other exemplified compounds from this series of benzimidazolone peptidomimetics include the following:



299537: C40 H44 F3 N9 O4

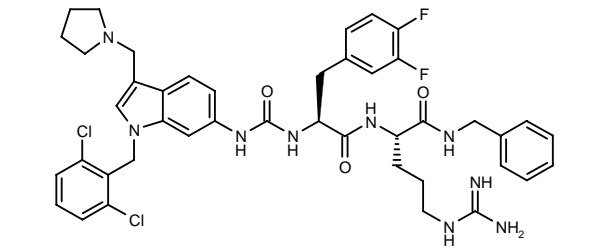
SOURCES – COR Therapeutics; Ortho-McNeil.

REFERENCES

1. Zhang, H.-C. et al. (COR Therapeutics, Inc.;Ortho-McNeil Pharmaceutical, Inc.) *Benzimidazolone peptidomimetics as thrombin receptor antagonists*. WO 0100659.

299538

N-[N-[1-(2,6-Dichlorobenzyl)-3-(1-pyrrolidinylmethyl)-1H-indol-6-yl]carbamoyl]-3,4-difluoro-L-phenylalanyl-L-arginine benzylamide



C43 H47 Cl2 F2 N9 O3; Mol wt: 846.8063

ACTION – Thrombin receptor (PAR-1) antagonist, potentially useful in the treatment of thrombosis, restenosis, hypertension, heart failure, arrhythmia, myocardial infarction, glomerulonephritis, inflammation, stroke, atherosclerosis, ischemic conditions, neurodegenerative disorders, angiogenic disorders and cancer. *In vitro*, compound gave IC₅₀ values of 0.02 and 0.29 μM in a PAR-1 binding assay and a thrombin-induced gel-filtered platelet aggregation assay, respectively. Other exemplified compounds from this series of indole peptidomimetics include the following:

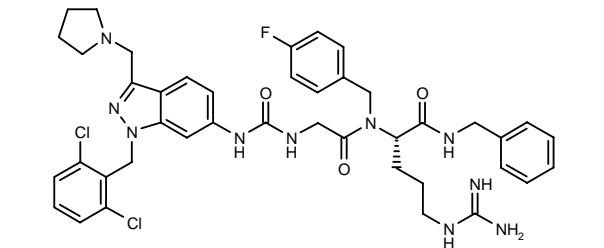
SOURCES – COR Therapeutics; Ortho-McNeil.

REFERENCES

1. Zhang, H.-C. et al. (Ortho-McNeil Pharmaceutical, Inc.;COR Therapeutics, Inc.) *Novel indole peptidomimetics as thrombin receptor antagonists*. WO 0100657.

299572

N-[N-[1-(2,6-Dichlorobenzyl)-3-(1-pyrrolidinylmethyl)-1H-indazol-6-yl]carbamoyl]glycyl-N²-(4-fluorobenzyl)-L-arginine benzylamide



C42 H47 Cl2 F N10 O3; Mol wt: 829.8043

ACTION – Thrombin receptor (PAR-1) antagonist, potentially useful in the treatment of thrombosis, restenosis, hypertension, heart failure, arrhythmia, myocardial infarction, glomerulonephritis, inflammation, stroke, atherosclerosis, ischemic conditions, neurodegenerative disorders, angiogenic disorders and cancer. A representative compound from a series of indole and indazole urea-peptoids.

SOURCES – COR Therapeutics; Ortho-McNeil.

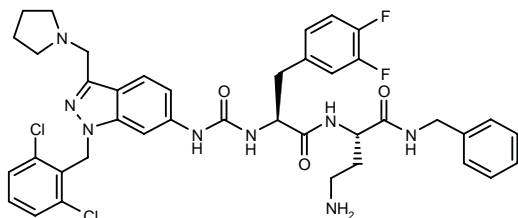
REFERENCES

1. McComsey, D.F. et al. (Ortho-McNeil Pharmaceutical, Inc.;COR Therapeutics, Inc.) *Indole and indazole urea-peptoids as thrombin receptor antagonists*. WO 0100576.

RWJ-58259

299524

N^1 -[3-Amino-1-(*S*)-(benzylcarbamoyl)propyl]- N^α -[N -[1-(2,6-dichlorobenzyl)-3-(1-pyrrolidinylmethyl)-1*H*-indazol-6-yl]carbamoyl]-3,4-difluoro-L-phenylalaninamide



C40 H42 Cl2 F2 N8 O3; Mol wt: 791.7268

ACTION – Potent and selective, second-generation indazole-based thrombin receptor (PAR-1) antagonist (IC_{50} = 0.15 μ M), an analogue of RWJ-56110 with improved cardiovascular safety. Compound strongly inhibited thrombin- and SFLLRN-NH₂-induced human platelet aggregation (IC_{50} = 0.37 and 0.11 μ M, respectively), as well as thrombin-induced aggregation of human and guinea pig platelet-rich plasma (IC_{50} = 8 and 7 μ M, respectively). Despite its strong *in vitro* activity, it was not effective in inhibiting thrombus formation in guinea pig arteriovenous shunt or photoactivation models following i.v. administration; it did, however, produce a moderate reduction in thrombus weight in the arteriovenous shunt model when delivered into the shunt. Compound was also found to inhibit rat aortic smooth muscle Ca²⁺ mobilization and proliferation (IC_{50} = 0.07 and 2.3 μ M, respectively) *in vitro* and to significantly reduce the intimal thickness after perivascular administration in rats undergoing balloon angioplasty. Potentially useful for the treatment or prevention of restenosis following balloon angioplasty or other cardiac interventions.

SOURCES – COR Therapeutics; R.W. Johnson.

REFERENCES

1. Zhang, H.-C. et al. (Ortho-McNeil Pharmaceutical, Inc.; COR Therapeutics, Inc.) *Novel indazole peptidomimetics as thrombin receptor antagonists*. WO 0100656.
2. Derian, C.K. et al. *Potential therapeutic applications of a selective thrombin receptor (PAR-1) antagonist*. Circulation 2000, 102(18, Suppl.): Abst 1472.
3. Maryanoff, B.E. et al. *Discovery and optimization of a novel of thrombin receptor (PAR-1) antagonists: Potent, selective peptide-mimetics based on indole and indazole templates*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 340.
4. Zhang, H.-C. et al. *Discovery and optimization of a novel series of thrombin receptor (PAR-1) antagonists: Potent, selective peptide mimetics based on indole and indazole templates*. J Med Chem 2001, 44(7): 1021.

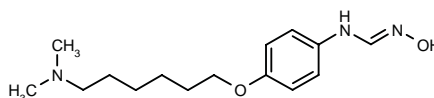
RENAL-UROLOGIC DRUGS

TREATMENT OF RENAL DISEASES

301922^{1,5}

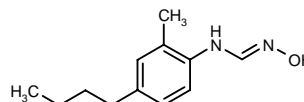
N^1 -[4-[6-(Dimethylamino)hexyloxy]phenyl]- N^2 -hydroxyformamide

N -[4-[6-(Dimethylamino)hexyloxy]phenyl]- N' -hydroxymethanimidamide



C15 H25 N3 O2; Mol wt: 279.3815

ACTION – 20-Hydroxyeicosatetraenoic acid (20-HETE) synthase inhibitor (IC_{50} = 18.7 nM) with improved aqueous solubility and selectivity over other cytochrome P-450 (CYP) enzymes compared to the parent 20-HETE synthase inhibitor **HET-0016**. Potentially useful for the treatment of renal and cerebrovascular diseases.



HET-0016 [301565]¹⁻⁵: C12 H18 N2 O

SOURCE – Taisho.

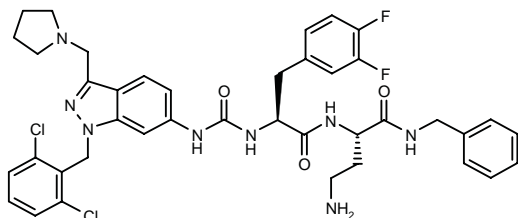
REFERENCES

1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Inhibitor for 20-HETE-yielding enzyme*. WO 0132164.
2. Kehl, F. et al. *Blockade of 20-HETE formation attenuates cerebral vasospasm after subarachnoid hemorrhage in the rat*. FASEB J 2001, 15(4, Part 1): Abst 151.22.
3. Miyata, N. et al. *HET0016, a potent and selective inhibitor of 20-HETE synthase*. FASEB J 2001, 15(4, Part 1): Abst 161.10.
4. Miyata, N. et al. *HET0016, a potent and selective inhibitor of 20-HETE synthesizing enzyme*. Br J Pharmacol 2001, 133(3): 325.
5. Sato, M. et al. *HET0016, a potent and selective 20-HETE synthase inhibitor*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 47.

RWJ-58259

299524

N^1 -[3-Amino-1-(*S*)-(benzylcarbamoyl)propyl]- N^α -[N -[1-(2,6-dichlorobenzyl)-3-(1-pyrrolidinylmethyl)-1*H*-indazol-6-yl]carbamoyl]-3,4-difluoro-L-phenylalaninamide



C40 H42 Cl2 F2 N8 O3; Mol wt: 791.7268

ACTION – Potent and selective, second-generation indazole-based thrombin receptor (PAR-1) antagonist (IC_{50} = 0.15 μ M), an analogue of RWJ-56110 with improved cardiovascular safety. Compound strongly inhibited thrombin- and SFLLRN-NH₂-induced human platelet aggregation (IC_{50} = 0.37 and 0.11 μ M, respectively), as well as thrombin-induced aggregation of human and guinea pig platelet-rich plasma (IC_{50} = 8 and 7 μ M, respectively). Despite its strong *in vitro* activity, it was not effective in inhibiting thrombus formation in guinea pig arteriovenous shunt or photoactivation models following i.v. administration; it did, however, produce a moderate reduction in thrombus weight in the arteriovenous shunt model when delivered into the shunt. Compound was also found to inhibit rat aortic smooth muscle Ca²⁺ mobilization and proliferation (IC_{50} = 0.07 and 2.3 μ M, respectively) *in vitro* and to significantly reduce the intimal thickness after perivascular administration in rats undergoing balloon angioplasty. Potentially useful for the treatment or prevention of restenosis following balloon angioplasty or other cardiac interventions.

SOURCES – COR Therapeutics; R.W. Johnson.

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1. Zhang, H.-C. et al. (Ortho-McNeil Pharmaceutical, Inc.; COR Therapeutics, Inc.) *Novel indazole peptidomimetics as thrombin receptor antagonists*. WO 0100656.
2. Derian, C.K. et al. *Potential therapeutic applications of a selective thrombin receptor (PAR-1) antagonist*. Circulation 2000, 102(18, Suppl.): Abstr 1472.
3. Maryanoff, B.E. et al. *Discovery and optimization of a novel of thrombin receptor (PAR-1) antagonists: Potent, selective peptide-mimetics based on indole and indazole templates*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abstr MEDI 340.
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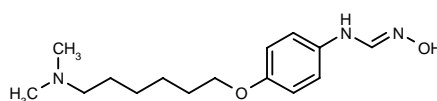
RENAL-UROLOGIC DRUGS

TREATMENT OF RENAL DISEASES

301922^{1,5}

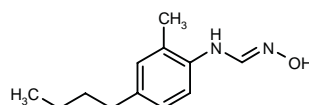
N^1 -[4-[6-(Dimethylamino)hexyloxy]phenyl]- N^2 -hydroxyformamide

N -[4-[6-(Dimethylamino)hexyloxy]phenyl]- N' -hydroxymethanimidamide



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HET-0016 [301565]¹⁻⁵: C12 H18 N2 O

SOURCE – Taisho.

REFERENCES

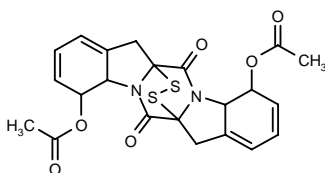
1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Inhibitor for 20-HETE-yielding enzyme*. WO 0132164.
2. Kehl, F. et al. *Blockade of 20-HETE formation attenuates cerebral vasospasm after subarachnoid hemorrhage in the rat*. FASEB J 2001, 15(4, Part 1): Abstr 151.22.
3. Miyata, N. et al. *HET0016, a potent and selective inhibitor of 20-HETE synthase*. FASEB J 2001, 15(4, Part 1): Abstr 161.10.
4. Miyata, N. et al. *HET0016, a potent and selective inhibitor of 20-HETE synthesizing enzyme*. Br J Pharmacol 2001, 133(3): 325.
5. Sato, M. et al. *HET0016, a potent and selective 20-HETE synthase inhibitor*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abstr MEDI 47.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

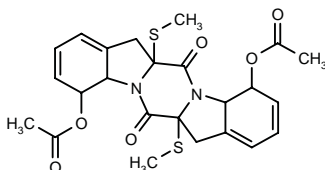
300118

4,11-Diacetoxy-4a,6a,11,11a,13a,14-hexahydro-7H,13H-6a,13a-epidithio-4H,6H-pyrazino[1,2-a:4,5-a']diindole-6,13-dione



C₂₂ H₂₀ N₂ O₆ S₂; Mol wt: 472.5400

ACTION – Anti-*Helicobacter pylori* agent isolated from *Rhizostilbella hibisci* strain JCM8210. Another compound isolated from the same source is:



300119: C₂₄ H₂₆ N₂ O₆ S₂

SOURCE – Yamanouchi.

REFERENCES

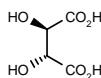
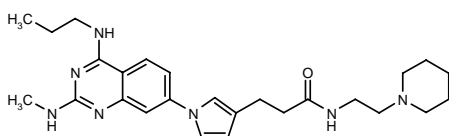
1. Taniguchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel dioxopiperazine derivs.* JP 2001011075.

AGENTS FOR IRRITABLE BOWEL SYNDROME

KF-66854

302306

3-[1-[2-(Methylamino)-4-(propylamino)quinazolin-7-yl]-1H-pyrrol-3-yl]-N-[2-(1-piperidinyl)ethyl]propionamide tartrate



C₂₆ H₃₇ N₇ O . C₄ H₆ O₆; Mol wt: 613.7117

ACTION – 5-HT₄ receptor agonist with nanomolar affinity for 5-HT₄ receptors (K_i = 55 nM) and agonist activity, measured by stimulation of cAMP production in rat esophageal muscularis mucosae (EC₅₀ = 450 nM) and relaxation of rat esophageal muscularis mucosae precontracted with carbachol (EC₅₀ = 27 nM). *In vivo*, compound was found to promote digestive motility in dogs. Potentially useful as a prokinetic agent for the treatment of gastrointestinal motor dysfunction such as gastroesophageal reflux disease (GERD), functional dyspepsia and irritable bowel syndrome (IBS).

SOURCE – Kyowa Hakko.

REFERENCES

1. Koshimura, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Quinazoline derivs.* WO 9950264.

2. Koshimura, H. et al. *Synthesis of quinazoline derivatives with 5-HT₄ agonist activity.* (2nd Report). 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)II-068.

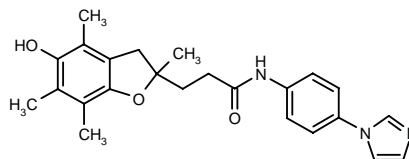
3. Nosaka, C. et al. *Pharmacological properties of KF66854, a novel 5-HT₄ receptor agonist with quinazoline structure, in vitro.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-195.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

A-2757

302095

3-(5-Hydroxy-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-2-yl)-N-[4-(1H-imidazol-1-yl)phenyl]propionamide



C₂₄ H₂₇ N₃ O₃; Mol wt: 405.4953

ACTION – Antioxidant proven to inhibit iron-induced lipid peroxidation in rat hepatic microsomes (IC₅₀ = 2.7 μM) and copper-induced peroxidation in human plasma LDL (IC₅₀ = 5.0 μM), effects comparable to those of probucol and PHB but approximately 10-fold less than those of troglitazone in rat liver microsomes. In a rat model of CCl₄-induced hepatopathy, oral doses of 1-3 mg/kg exhibited a strong protective effect greater than probucol, vitamin E acetate, troglitazone and malotilate at 3-100 mg/kg p.o. Moreover, in a mouse model of acetaminophen-induced hepatopathy, it markedly inhibited lipid peroxide production and hepatic damage when given orally at a dose of 3 mg/kg, and was more effective than the above-mentioned drugs. Compound was also found to protect mice in a model of cisplatin-induced nephropathy. Potentially useful for the treatment of hepatic and renal disorders involving active oxygen species or free radicals.

SOURCE – Nippon Soda.

REFERENCES

1. Umeda, N. et al. (Nippon Soda Co., Ltd.) *Phenylazole cpds., process for producing the same and drugs for hyperlipemia*. EP 1101759, JP 2000281656, JP 2000281658, JP 2000290280, WO 0006550.

2. Mochizuki, N. et al. *A novel antioxidant A-2757 (1). Structure-activity relationship*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-044.

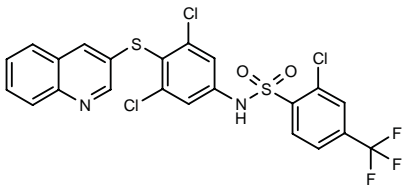
3. Mochizuki, N. et al. *A novel antioxidant A-2757 (2). Pharmacological effects*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-045.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

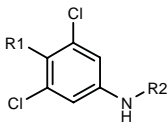
299301

2-Chloro-*N*-[3,5-dichloro-4-(3-quinolinylsulfanyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide



C22 H12 Cl3 F3 N2 O2 S2; Mol wt: 563.8338

ACTION – Modulator of the peroxisome proliferator-activated receptor PPAR γ that acts as an agonist or antagonist depending on the biological environment. It exhibited an IC₅₀ < 1 μ M in a PPAR γ binding assay using [³H]-BRL-49653 as radioligand and demonstrated antidiabetic activity by lowering serum glucose levels by > 20% in KKA^y mice when administered in the diet at 30 mg/kg. This compound is useful for the treatment of type 2 diabetes, as well as lipid metabolism disorders and inflammatory conditions. Other exemplified compounds are:



Compound	R1	R2	Formula
299303	3-quinolyl-O	2,4-(Cl)2-PhSO2	C ₂₁ H ₁₂ Cl ₄ N ₂ O ₃ S
299306	6-Cl-2-benzothiazolyl-NH	2-Cl-4-CF3-PhSO2	C ₂₀ H ₁₀ Cl ₄ F ₃ N ₃ O ₂ S ₂
299307	6-Me-2-benzothiazolyl-NH	2-Cl-4-CF3-PhSO2	C ₂₁ H ₁₃ Cl ₃ F ₃ N ₃ O ₂ S ₂
299311	6-Cl-2-benzothiazolyl-O	H	C ₁₃ H ₇ Cl ₃ N ₂ OS
299312	6-Cl-2-benzothiazolyl-O	2-Cl-4-CF3-PhSO2	C ₂₀ H ₉ Cl ₄ F ₃ N ₂ O ₃ S ₂

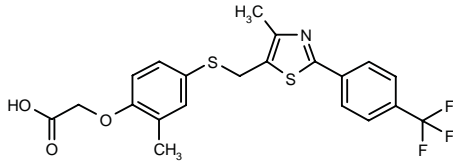
SOURCES – Japan Tobacco; Tularik.

REFERENCES

1. McGee, L.R. et al. (Tularik Inc.;Japan Tobacco Inc.) *Cpds. for the modulation of PPAR γ activity*. WO 0100579.

299373

2-[2-Methyl-4-[4-methyl-2-[4-(trifluoromethyl)-phenyl]thiazol-5-ylmethylsulfanyl]phenoxy]acetic acid



C21 H18 F3 N O3 S2; Mol wt: 453.5032

ACTION – Selective human peroxisome proliferator activated receptor PPAR δ agonist with potential for the treatment of dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, diabetes, insulin resistance, hyperlipidemia, obesity, anorexia and bulimia. Compound gave a pK_i value > 6.5 in a PPAR δ binding assay and showed at least 50% activation of hPPAR δ at a concentration of 0.1 μ M or less in a transactivation assay. Compound was tested *in vivo* in a 6-month dose-escalation study in obese rhesus monkeys and was found to raise HDL cholesterol at each dose tested (0.1, 0.3, 1 and 3 mg/kg b.i.d. p.o.), HDL cholesterol increasing by more than 40% at 3 mg/kg; furthermore, it was shown to decrease serum triglyceride concentrations by more than 30%, insulin by more than 20% and serum fibrinogen concentrations by 10-20%. A specifically claimed compound from a series of thiazole and oxazole derivatives.

SOURCE – GlaxoSmithKline.

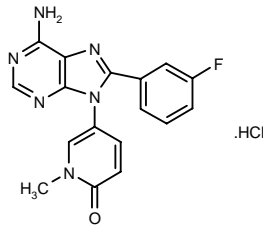
REFERENCES

1. Chao, E.Y.-H. et al. (Glaxo Group Ltd.) *Thiazole and oxazole derivs. and their pharmaceutical use*. WO 0100603.

299710

5-[6-Amino-8-(3-fluorophenyl)-9*H*-purin-9-yl]-1-methylpyridin-2(1*H*)-one hydrochloride

5-[8-(3-Fluorophenyl)adenin-9-yl]-1-methylpyridin-2(1*H*)-one hydrochloride



C17 H13 F N6 O . HCl; Mol wt: 372.7896

REFERENCES

1. Umeda, N. et al. (Nippon Soda Co., Ltd.) *Phenylazole cpds., process for producing the same and drugs for hyperlipemia*. EP 1101759, JP 2000281656, JP 2000281658, JP 2000290280, WO 0006550.

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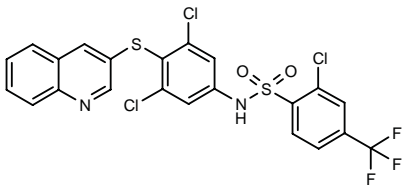
3. Mochizuki, N. et al. *A novel antioxidant A-2757 (2). Pharmacological effects*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-045.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

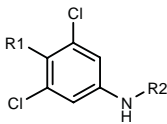
299301

2-Chloro-*N*-[3,5-dichloro-4-(3-quinolinylsulfanyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide



C22 H12 Cl3 F3 N2 O2 S2; Mol wt: 563.8338

ACTION – Modulator of the peroxisome proliferator-activated receptor PPAR γ that acts as an agonist or antagonist depending on the biological environment. It exhibited an IC₅₀ < 1 μ M in a PPAR γ binding assay using [³H]-BRL-49653 as radioligand and demonstrated antidiabetic activity by lowering serum glucose levels by > 20% in KKA^y mice when administered in the diet at 30 mg/kg. This compound is useful for the treatment of type 2 diabetes, as well as lipid metabolism disorders and inflammatory conditions. Other exemplified compounds are:



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299307	6-Me-2-benzothiazolyl-NH	2-Cl-4-CF3-PhSO2	C ₂₁ H ₁₃ Cl ₃ F ₃ N ₃ O ₂ S ₂
299311	6-Cl-2-benzothiazolyl-O	H	C ₁₃ H ₇ Cl ₃ N ₂ OS
299312	6-Cl-2-benzothiazolyl-O	2-Cl-4-CF3-PhSO2	C ₂₀ H ₉ Cl ₄ F ₃ N ₂ O ₃ S ₂

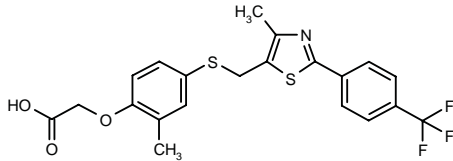
SOURCES – Japan Tobacco; Tularik.

REFERENCES

1. McGee, L.R. et al. (Tularik Inc.;Japan Tobacco Inc.) *Cpds. for the modulation of PPAR γ activity*. WO 0100579.

299373

2-[2-Methyl-4-[4-methyl-2-[4-(trifluoromethyl)-phenyl]thiazol-5-ylmethylsulfanyl]phenoxy]acetic acid



C21 H18 F3 N O3 S2; Mol wt: 453.5032

ACTION – Selective human peroxisome proliferator activated receptor PPAR δ agonist with potential for the treatment of dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, diabetes, insulin resistance, hyperlipidemia, obesity, anorexia and bulimia. Compound gave a pK_i value > 6.5 in a PPAR δ binding assay and showed at least 50% activation of hPPAR δ at a concentration of 0.1 μ M or less in a transactivation assay. Compound was tested *in vivo* in a 6-month dose-escalation study in obese rhesus monkeys and was found to raise HDL cholesterol at each dose tested (0.1, 0.3, 1 and 3 mg/kg b.i.d. p.o.), HDL cholesterol increasing by more than 40% at 3 mg/kg; furthermore, it was shown to decrease serum triglyceride concentrations by more than 30%, insulin by more than 20% and serum fibrinogen concentrations by 10-20%. A specifically claimed compound from a series of thiazole and oxazole derivatives.

SOURCE – GlaxoSmithKline.

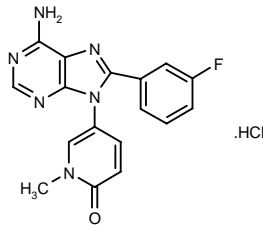
REFERENCES

1. Chao, E.Y.-H. et al. (Glaxo Group Ltd.) *Thiazole and oxazole derivs. and their pharmaceutical use*. WO 0100603.

299710

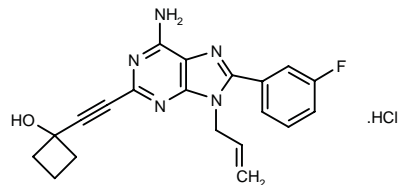
5-[6-Amino-8-(3-fluorophenyl)-9*H*-purin-9-yl]-1-methylpyridin-2(1*H*)-one hydrochloride

5-[8-(3-Fluorophenyl)adenin-9-yl]-1-methylpyridin-2(1*H*)-one hydrochloride



C17 H13 F N6 O . HCl; Mol wt: 372.7896

ACTION – Agent for the treatment of diabetes mellitus and complications of diabetes with adenosine A₂ receptor-antagonist activity, as demonstrated in binding assays by a K_i value of 0.0032 μM for A_{2A} receptors. In addition, compound was shown to inhibit NECA-stimulated cAMP production in CHOK1 cells expressing the human A_{2B} receptor (IC₅₀ = 0.011 μM), as well as NECA-stimulated glucose production in rat primary cultured hepatocytes (IC₅₀ = 0.0076 μM). When tested *in vivo* in diabetic KKA^y/Ta Jcl mice, it significantly lowered blood glucose levels at 10 mg/kg p.o. Another compound from this series of fused imidazole derivatives is:



299711: C20 H18 F N5 O . HCl

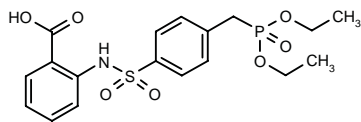
SOURCE – Eisai.

REFERENCES

1. Asano, O. et al. (Eisai Co., Ltd.) *Fused imidazole cpds. and remedies for diabetes mellitus*. WO 0102400.

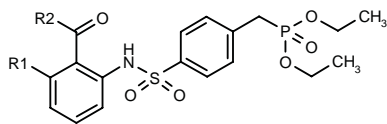
300054

2-[4-(Diethoxyphosphorylmethyl)phenylsulfonamido]-benzoic acid



C18 H22 N O7 P S; Mol wt: 427.4118

ACTION – Hypoglycemic agent proven to produce a 43% decrease in blood sugar levels in dexamethasone-treated rats at 100 mg/kg p.o. Other exemplified compounds from this series of phosphonic acid derivatives include the following:



Compound	R1	R2	Formula
300055	Cl	NHMe	C ₁₉ H ₂₄ ClN ₂ O ₆ PS
300056	H	4-morpholinyl-CH ₂ CH ₂ NH	C ₂₄ H ₃₄ N ₃ O ₇ PS
300057	H	Me	C ₁₉ H ₂₄ N ₂ O ₆ PS

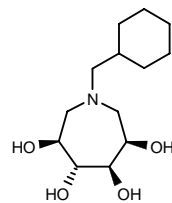
SOURCE – Otsuka.

REFERENCES

1. Miyata, K. et al. (Otsuka Pharmaceutical Co., Ltd.) *Phosphonic acid diester derivs*. JP 2001002687.

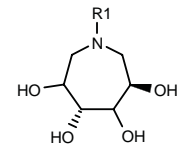
300070

1-(Cyclohexylmethyl)perhydroazepine-3(R),4(R),5(R),6(S)-tetrol



C13 H25 N O4; Mol wt: 259.3435

ACTION – Antidiabetic agent that acts by selectively inhibiting bovine kidney α-fucosidase (IC₅₀ = 0.025 μg/ml) over α-glucosidase (*Bacillus stearothermophilus*, IC₅₀ = 10 μg/ml), β-glucosidase (*Caldocellum saccharolytium*, IC₅₀ = 6 μg/ml), α-galactosidase (green coffee beans, IC₅₀ = 4 μg/ml), β-galactosidase (*Aspergillus niger*, IC₅₀ = 10 μg/ml) and α-mannosidase (Jack beans, IC₅₀ = 1.3 μg/ml). Other exemplified compounds from this series of N-substituted azepane derivatives include the following:



Compound	R1	Isomer	Formula
300071	CH2CH2OH	4R,6S	C ₈ H ₁₇ NO ₅
300073	CH2CH2OH	4S,6S	C ₈ H ₁₇ NO ₅
300074	CH2CH2OH	4R,6R	C ₈ H ₁₇ NO ₅
300076	(CH2)3OH	4S,6S	C ₉ H ₁₉ NO ₅
300079	6-deoxy-D-glucopyranos-6-yl	4R,6S	C ₁₂ H ₂₃ NO ₉
300080	6-deoxy-D-glucopyranos-6-yl	4R,6R	C ₁₂ H ₂₃ NO ₉

SOURCE – Kikkoman.

REFERENCES

1. Kasai, K. et al. (Kikkoman Corp.) *N-Substd. azepane derivs. and their salts*. JP 2001002648.

300151

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys-NH₂

C215 H347 N61 O65 S; Mol wt: 4858.5340

ACTION – Hypoglycemic agent, a representative compound from a series of peptide conjugates comprising variants of the GLP-1 or exendin-4 polypeptides that exhibit increased stability. Compound was shown to dose-dependently decrease blood glucose levels in *ob/ob* mice at 10-1000 μg/animal p.o.; significant reductions in glucose levels were also observed following administration of an dose of 100 μg/animal i.p. In addition, it was also effective in an oral glucose tolerance test (OGTT) in diabetic *db/db* mice, with a duration of action up to 18 h at 100 nmol/kg i.p. Other exemplified peptides include the following:

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-NH₂

300152: C179 H275 N49 O59 S

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Lys-Lys-Lys-Lys-Lys-NH₂

300153: C184 H296 N52 O51

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-N^ε-(hexadecanoyl)-Lys-Lys-Lys-Lys-Lys-NH₂

300154: C206 H338 N54 O53

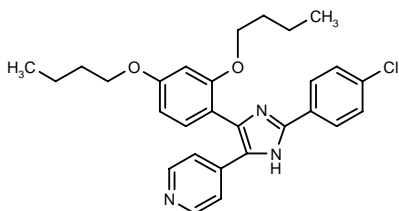
SOURCE – Zealand Pharmaceuticals.

REFERENCES

1. Larsen, B.D. et al. (Zealand Pharmaceuticals A/S) *Peptides that lower blood glucose levels*. EP 1076066, WO 0104156.

301980

4-[2-(4-Chlorophenyl)-4-(2,4-dibutoxyphenyl)-1*H*-imidazol-5-yl]pyridine



C28 H30 Cl N3 O2; Mol wt: 476.0170

ACTION – Selective nonpeptide glucagon receptor antagonist with an IC₅₀ value of 0.0065 μM for the human glucagon receptor in the absence of Mg²⁺ and of 0.053 μM in the presence of physiological concentrations of Mg²⁺. Compound showed only marginal p38 kinase-inhibitory activity at 40 μM. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Merck & Co.

REFERENCES

1. Chang, L.L. (Merck & Co., Inc.) *Triaryl substd. imidazoles as glucagon antagonists*. EP 0959886, JP 2000514088, US 5880139, WO 9822109.

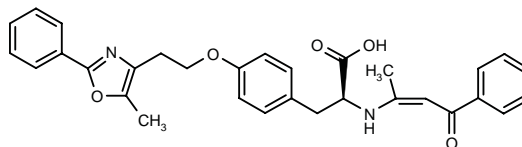
2. Chang, L.L. et al. *Selective, non-peptide antagonists for the glucagon receptor: Substituted imidazoles*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 237.

GW-409544X

278306

N-[1-Methyl-3-oxo-3-phenyl-1(*Z*)-propenyl]-*O*-[2-(5-methyl-2-phenyloxazol-4-yl)ethyl]-*L*-tyrosine

GW-544



C31 H30 N2 O5; Mol wt: 510.5870

ACTION – Potent and selective dual agonist at the peroxisome proliferator-activated receptors PPAR_γ and PPAR_α, proven to lower plasma triglycerides and LDL cholesterol in obese rhesus monkeys. Phase I clinical studies in healthy volunteers demonstrated that compound given as single doses ranging from 2.5 to 17.5 mg induced a dose-dependent decrease in serum triglycerides and nonesterified fatty acids (up to 61 and 45%, respectively); no change was seen in serum glucose and insulin levels over 24 h compared to placebo or baseline, and GW-409544X was well tolerated. Potentially useful for the treatment of type 2 diabetes, particularly the dyslipidemia seen in this disorder.

SOURCES – Ligand; GlaxoSmithKline.

REFERENCES

1. Collins, J.L. et al. (Glaxo Group Ltd.) *Substd. oxazoles and thiazoles derivs. as hPPAR γ and hPPAR α activators*. EP 1102757, WO 0008002.

2. Mudd, P.N. Jr. and Young, M.A. *Prospective comparison of pharmacokinetic/pharmacodynamic (PK/PD) model predictions and actual phase I results for GW409544X, a PPAR γ/α agonist*. Clin Pharmacol Ther 2001, 69(2): Abst PII-107.

3. Oplinger, J.A. et al. *Discovery of potent PPARα and PPARγ dual agonist*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 238.

4. Young, M.A. et al. *A new PPARγ/α agonist: First time administration to healthy male volunteers*. Clin Pharmacol Ther 2001, 69(2): Abst PII-42.

5. *Product development pipeline*. Glaxo Wellcome Product Pipeline 2000, Feb 1.

6. *Product development pipeline*. GlaxoSmithKline Product Pipeline 2001, February.

7. *Product development status*. Ligand Pharmaceuticals Product Pipeline 1999.

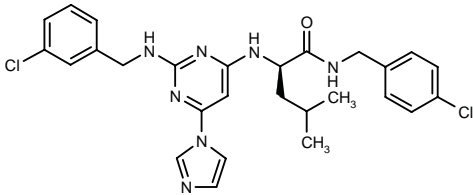
8. *Two compounds resulting from Ligand-Glaxo Wellcome collaboration advance through the pipeline*. DailyDrugNews.com (Daily Essentials) 1999, Oct 29.

9. *Two new drugs added to the R&D pipeline at Glaxo Wellcome*. DailyDrugNews.com (Daily Essentials) 1999, July 16.

TREATMENT OF DIABETIC
COMPLICATIONS

300393

N′-(4-Chlorobenzyl)-*N*′-[2-(3-chlorobenzylamino)-6-(1*H*-imidazol-1-yl)pyrimidin-4-yl]-*D*-leucinamide



C27 H29 Cl2 N7 O; Mol wt: 538.4801

ACTION – A representative compound from a series of pyrimidines, triazines and anilines with bradykinin B₁ receptor-antagonist activity, potentially useful for the treatment of diseases associated with inappropriate or excessive bradykinin receptor activity such as diabetic vasculopathy, postcapillary resistance or diabetic symptoms associated with insulitis, inflammation, pain, hyperalgesia, asthma, rhinitis, septic shock, atherosclerosis and multiple sclerosis.

SOURCE – Pharmacopeia.

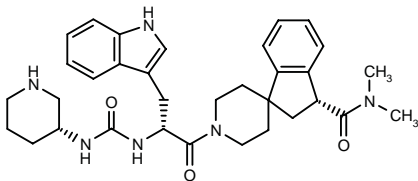
REFERENCES

1. Baldwin, J.J. et al. (Pharmacopeia, Inc.) *Bradykinin B₁ receptor antagonists*. WO 0105783.

TREATMENT OF GROWTH HORMONE
SECRETION DISORDERS

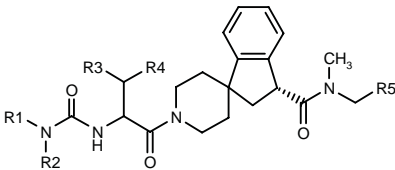
300203

1′-[3-(1*H*-Indol-3-yl)-2(*R*)-[3-[3(*R*)-piperidinyl]ureido]-propionyl]-*N,N*-dimethylspiro[indane-1,4′-piperidine]-3(*R*)-carboxamide



C33 H42 N6 O3; Mol wt: 570.7338

ACTION – Growth hormone (GH) secretagogue with potential for the treatment of diseases or conditions which would benefit from the anabolic effects of increased GH levels, such as osteoporosis, catabolic illness, immune deficiency, bone fracture, musculoskeletal impairment in the elderly, GH deficiency in adults or children, short stature in children, obesity, sleep disorders, cachexia and protein loss due to chronic illness such as AIDS or cancer, and recovery from major surgery, wounds or burns. Other specifically claimed compounds from this series of amido spiro piperidines include the following:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
300204	3(R)-pyrrolidinyl	H	3-indolyl	H	H	2R	C ₃₂ H ₄₀ N ₆ O ₃
300205	3(R)-Pip	Me	3-indolyl	Me	H	2R,3R	C ₃₅ H ₄₆ N ₆ O ₃
300206	CH ₂ CH ₂ NH ₂	H	3-indolyl	Me	H	2R,3R	C ₃₁ H ₄₀ N ₆ O ₃
300207	CH ₂ CH ₂ NHMe	H	3-indolyl	Me	H	2R,3R	C ₃₂ H ₄₂ N ₆ O ₃
300208	3(R)-Pip	Me	3-indolyl	Me	Et	2R,3R	C ₃₇ H ₅₀ N ₆ O ₃
300209	3(R)-Pip	H	1-Me-3-indolyl	H	H		C ₃₄ H ₄₄ N ₆ O ₃
300210	3(R)-Pip	H	2-Naph	H	H	2R	C ₃₅ H ₄₃ N ₆ O ₃

SOURCE – Merck & Co.

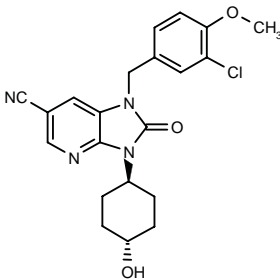
REFERENCES

1. Tata, J.R. and Patchett, A.A. (Merck & Co., Inc.) *Amido spiro piperidines promote the release of growth hormone*. WO 0104119.

TREATMENT OF MALE SEXUAL
DYSFUNCTION

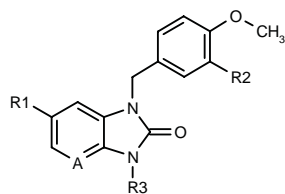
300409

trans-1-(3-Chloro-4-methoxybenzyl)-3-(4-hydroxycyclohexyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile



C21 H21 Cl N4 O3; Mol wt: 412.8749

ACTION – Potent inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ < 10 nM against human platelet PDE5), potentially useful for treating and/or preventing cGMP-PDE-mediated diseases, i.e., angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, erectile dysfunction, diabetic complications and incontinence. A pharmaceutical composition for the treatment of erectile dysfunction and impotence is also specifically claimed. Other benzimidazolone derivatives include the following:



Compound	R1	R2	R3	A	Formula
300410	CN	Cl	1-(t-BuOCO)-3-pyrrolidinyl	CH	C ₂₅ H ₂₇ ClN ₄ O ₄
300411	CN	CN	trans-4-OH-cyclohexyl	CH	C ₂₃ H ₂₂ N ₄ O ₃
300412	CN	Cl	(3at,5r,7at)-2-i-Pr-perhydro-1,3-benzodioxol-5-yl	CH	C ₂₆ H ₂₆ ClN ₃ O ₄
300413	NO2	NO2	trans-4-OH-cyclohexyl	CH	C ₂₁ H ₂₂ N ₄ O ₇
300414	CF3	Cl	(R)-CH(Me)CH2OH	N	C ₁₈ H ₁₇ ClF ₃ N ₃ O ₃
300415	CN	Cl	1-Me-4-Pip	CH	C ₂₂ H ₂₃ ClN ₄ O ₂
300416	CF3	Cl	5-benzimidazolyl	CH	C ₂₃ H ₁₆ ClF ₃ N ₄ O ₂
300586	CN	Br	trans-4-OH-cyclohexyl	N	C ₂₁ H ₂₁ BrN ₄ O ₃
300587	CN	Cl	cis-4-OH-cyclohexyl	N	C ₂₁ H ₂₁ ClN ₄ O ₃

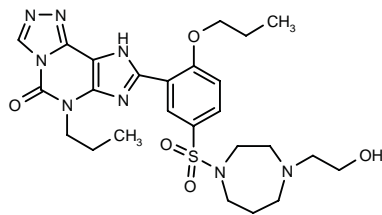
SOURCE – Fujisawa.

REFERENCES

1. Sawada, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Benzimidazolone derivs. and their use as phosphodiesterase inhibitors*. WO 0105770.

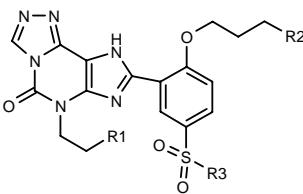
300499

8-[5-[4-(2-Hydroxyethyl)perhydro-1,4-diazepin-1-yl-sulfonyl]-2-propoxyphenyl]-6-propyl-6,9-dihydro-5H-[1,2,4]triazolo[3,4-*l*]purin-5-one



C25 H34 N8 O5 S; Mol wt: 558.6606

ACTION – Selective inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 0.34 nM against enzyme from human platelets), potentially useful in the treatment of hypertension, angina, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, peripheral vascular disease, vascular disorders, stroke, bronchitis, asthma, allergic rhinitis, glaucoma, male erectile dysfunction, female sexual dysfunction and gut motility disorders. Other exemplified compounds from this series of 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*l*]purin-5-one derivatives include the following:



Compound	R1	R2	R3	Formula
300501	H	H	4-Me-1-Piz	C ₂₂ H ₂₈ N ₈ O ₄ S
300502	H	Me	4-Me-1-Piz	C ₂₃ H ₃₀ N ₈ O ₄ S
300503	Me	H	4-Pyr-NH	C ₂₃ H ₂₄ N ₈ O ₄ S
300504	Me	H	4-Me-1-Piz	C ₂₃ H ₃₀ N ₈ O ₄ S
300505	Me	H	4-Me-perhydro-1,4-diazepin-1-yl	C ₂₄ H ₃₂ N ₈ O ₄ S
300506	Me	H	4-(CH2CH2OH)-1-Piz	C ₂₄ H ₃₂ N ₈ O ₅ S
300507	Et	H	4-(CH2CH2OH)-1-Piz	C ₂₅ H ₃₄ N ₈ O ₅ S
300508	Me	H	3(S)-Me-1-Piz	C ₂₃ H ₃₀ N ₈ O ₄ S
300509	Me	H	(1S,4S)-5-Me-2,5-diaza-bicyclo[2.2.1]hept-2-yl	C ₂₄ H ₃₀ N ₈ O ₄ S
300510	Me	H	3-[N(Me)2CH2]-1-azetidiny	C ₂₄ H ₃₂ N ₈ O ₄ S
300511	Me	H	3(R),5(S)-(Me)2-1-Piz	C ₂₄ H ₃₂ N ₈ O ₄ S
300512	Me	H	NHCH2C(Me)2CH2N(Me)2	C ₂₅ H ₃₆ N ₈ O ₄ S
300513	Me	H	4-[HOCH2C(Me)2]-1-Piz	C ₂₆ H ₃₆ N ₈ O ₅ S
300514	Et	H	4-[HOCH2C(Me)2]-1-Piz	C ₂₇ H ₃₈ N ₈ O ₅ S

SOURCE – Almirall Prodesfarma.

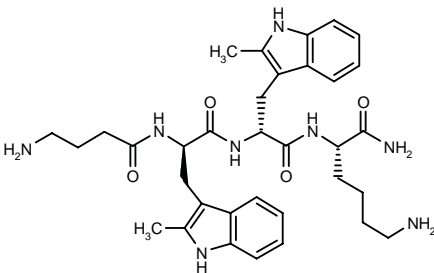
REFERENCES

1. Gracia Ferrer, J. et al. (Almirall Prodesfarma, SA) *8-Phenyl-6,9-dihydro-[1,2,4]-triazolo[3,4-*i*]purin-5-one derivs*. WO 0107441.

EP-80661

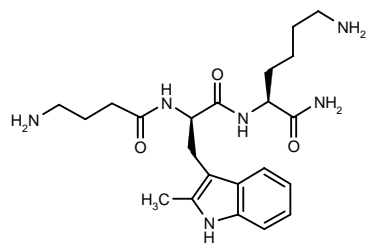
290665

N-(4-Aminobutyl)-2-methyl-D-tryptophyl-2-methyl-D-tryptophyl-L-lysineamide



C34 H46 N8 O4; Mol wt: 630.7894

ACTION – Peptide analogue of the growth hormone (GH)-releasing peptide hexarelin, proven to induce penile erection in rats when injected into the paraventricular nucleus of the hypothalamus (1 µg). Concomitantly, compound induced an increase of NO₂⁻ and NO₃⁻ in paraventricular nuclei, which was not prevented by an oxytocin receptor antagonist. In contrast, hexarelin had not effect on either penile erection or paraventricular NO₂⁻ and NO₃⁻. Potentially useful for the treatment of erectile dysfunction. Another GH-releasing peptide analogue is:



EP-91071 [290668]: C22 H34 N6 O3

SOURCE – Europeptides.

REFERENCES

1. Argiolas, A. and Deghenghi, R. (Asta Medica AG) *Peptides for treatment of erectile dysfunction*. US 6211156, WO 0134171.

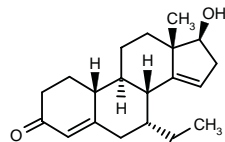
2. Argiolas, A. et al. *Peptide analogs of the GH-releasing peptide hexarelin induce penile erection in male rats: Structure-activity studies and comparison with apomorphine, oxytocin and N-methyl-D-aspartic acid*. 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 1121.

3. Melis, M.R. et al. *Penile erection induced by EP 80661 and other hexarelin peptide analogues: Involvement of paraventricular nitric oxide*. Eur J Pharmacol 2001, 411(3): 305.

CONTRACEPTIVES

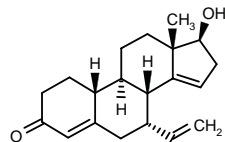
300347

7 α -Ethyl-17 β -hydroxyestra-4,14-dien-3-one



C20 H28 O2; Mol wt: 300.4392

ACTION – An orally active androgen with good metabolic stability. The compound inhibited serum LH in male castrated rats (ED₅₀ = 0.2 mg/kg p.o.) and exhibited a half-life of 157 min in human hepatocytes. Potentially useful for treating androgen insufficiency and in male contraception. Another exemplified 19-nortestosterone derivative is:



300348: C20 H26 O2

SOURCE – Akzo Nobel.

REFERENCES

1. Loozen, H.J.J. et al. (Akzo Nobel N.V.) *Orally active androgens*. WO 0105806.

DERMATOLOGIC DRUGS

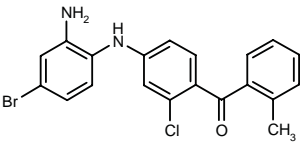
ACNE THERAPY

EO-1428

300394

1-[4-(2-Amino-4-bromophenylamino)-2-chlorophenyl]-1-(2-methylphenyl)methanone

4-(2-Amino-4-chlorophenylamino)-2-chloro-2'-methylbenzophenone



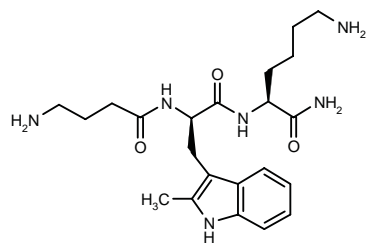
C20 H16 Br Cl N2 O; Mol wt: 415.7164

ACTION – Topical agent for the treatment and prevention of acne and related skin disorders, further reported to exhibit potential as an MAP kinase inhibitor and in the treatment of diseases associated with IL-1 β and TNF- α secretion. Compound was effective in the oxazolone-induced contact dermatitis model and the TPA-induced ear inflammation model in mice following topical administration, being clearly more potent than erythromycin, azelaic acid, benzoyl peroxide and *all-trans*-retinoic acid. In addition, it was shown to be effective in the rhino mouse model when tested at a concentration of 1.5% (67.4% reduction in the number of utriculi and 203% increase in epidermal thickness), being similar in potency to benzoyl peroxide at 5-10%, but being devoid of the skin irritation caused by the latter. A representative compound from a series of aminobenzophenones.

SOURCE – Leo.

REFERENCES

1. Ottosen, E.R. and Björklung, F. (Leo Pharmaceutical Products Ltd. A/S) *Novel aminobenzophenones*. WO 0105744.



EP-91071 [290668]: C22 H34 N6 O3

SOURCE – Europeptides.

REFERENCES

1. Argiolas, A. and Deghenghi, R. (Asta Medica AG) *Peptides for treatment of erectile dysfunction*. US 6211156, WO 0134171.

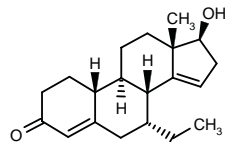
2. Argiolas, A. et al. *Peptide analogs of the GH-releasing peptide hexarelin induce penile erection in male rats: Structure-activity studies and comparison with apomorphine, oxytocin and N-methyl-D-aspartic acid*. 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 1121.

3. Melis, M.R. et al. *Penile erection induced by EP 80661 and other hexarelin peptide analogues: Involvement of paraventricular nitric oxide*. Eur J Pharmacol 2001, 411(3): 305.

CONTRACEPTIVES

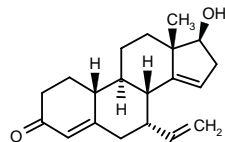
300347

7 α -Ethyl-17 β -hydroxyestra-4,14-dien-3-one



C20 H28 O2; Mol wt: 300.4392

ACTION – An orally active androgen with good metabolic stability. The compound inhibited serum LH in male castrated rats (ED₅₀ = 0.2 mg/kg p.o.) and exhibited a half-life of 157 min in human hepatocytes. Potentially useful for treating androgen insufficiency and in male contraception. Another exemplified 19-nortestosterone derivative is:



300348: C20 H26 O2

SOURCE – Akzo Nobel.

REFERENCES

1. Loozen, H.J.J. et al. (Akzo Nobel N.V.) *Orally active androgens*. WO 0105806.

DERMATOLOGIC DRUGS

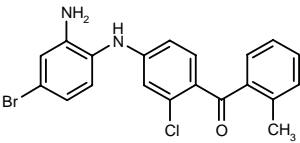
ACNE THERAPY

EO-1428

300394

1-[4-(2-Amino-4-bromophenylamino)-2-chlorophenyl]-1-(2-methylphenyl)methanone

4-(2-Amino-4-chlorophenylamino)-2-chloro-2'-methylbenzophenone



C20 H16 Br Cl N2 O; Mol wt: 415.7164

ACTION – Topical agent for the treatment and prevention of acne and related skin disorders, further reported to exhibit potential as an MAP kinase inhibitor and in the treatment of diseases associated with IL-1 β and TNF- α secretion. Compound was effective in the oxazolone-induced contact dermatitis model and the TPA-induced ear inflammation model in mice following topical administration, being clearly more potent than erythromycin, azelaic acid, benzoyl peroxide and *all-trans*-retinoic acid. In addition, it was shown to be effective in the rhino mouse model when tested at a concentration of 1.5% (67.4% reduction in the number of utriculi and 203% increase in epidermal thickness), being similar in potency to benzoyl peroxide at 5-10%, but being devoid of the skin irritation caused by the latter. A representative compound from a series of aminobenzophenones.

SOURCE – Leo.

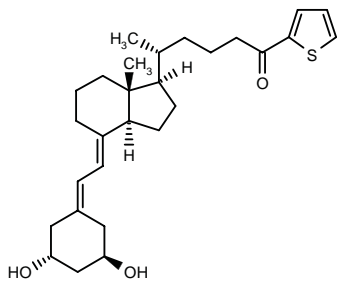
REFERENCES

1. Ottosen, E.R. and Björklung, F. (Leo Pharmaceutical Products Ltd. A/S) *Novel aminobenzophenones*. WO 0105744.

ANTIPSORIATICS

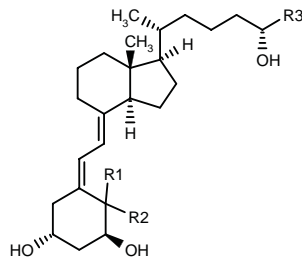
300539

5(R)-[(1*R*,3*R*,7*E*,17β)-1,3-Dihydroxy-9,10-secoestra-5,7-dien-17-yl]-1-(2-thienyl)hexan-1-one



C28 H40 O3 S; Mol wt: 456.6870

ACTION – Antiproliferative agent, a vitamin D derivative that exhibits > 350-fold lower hypercalcemic activity than calcitriol, while exhibiting only 12-fold lower affinity for the vitamin D receptor and 2-fold lower differentiation-inducing activity in HL-60 cells compared to calcitriol. Compound is reported to possess improved metabolic stability as compared to structurally related compounds, thus being suitable for systemic administration. Potentially useful for the treatment of hyperproliferative disorders such as psoriasis, acne, pruritus and cancer, as well as osteoporosis, autoimmune, inflammatory and neuro-degenerative disorders. Within this series of vitamin D derivatives with cyclic substructures in the side-chains, the following are also included:



Compound	R1	R2	R3	Formula
300540	H	H	4-oxazolyl	C ₂₇ H ₄₁ NO ₄
300541	-CH2-		4-oxazolyl	C ₂₈ H ₄₁ NO ₄
300542	H	H	2-thienyl	C ₂₈ H ₄₂ O ₃ S
300543	-CH2-		2-thiazolyl	C ₂₈ H ₄₁ NO ₃ S

SOURCE – Schering AG.

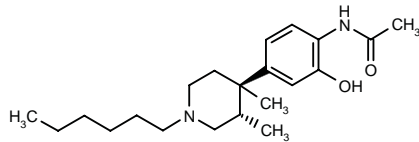
REFERENCES

1. Steinmeyer, A. et al. (Schering AG) *New vitamin D derivs. with cyclic substructures in the side chains, method and intermediates for their production and their use in the preparation of medicaments.* DE 19935771, WO 0107405..

MISCELLANEOUS
DERMATOLOGIC DRUGS

299754

(±)-*trans*-*N*-[4-[1-Hexyl-3,4-dimethylpiperidin-4-yl]-2-hydroxyphenyl]acetamide



C21 H34 N2 O2; Mol wt: 346.5116

ACTION – Agent for the prevention or treatment of pruritus reported to inhibit hind leg scratching behavior induced by s.c. injection of 5-methoxytryptamine in rats following s.c. administration. A representative compound from a series of 4-arylpiperidine derivatives.

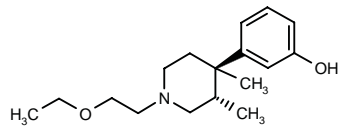
SOURCE – Pfizer.

REFERENCES

1. Bronk, B.S. et al. (Pfizer Ltd.;Pfizer Inc.) *4-Arylpiperidine derivs. for the treatment of pruritus.* EP 1072596, JP 2001019673.

299756

(±)-*trans*-3-[1-(2-Ethoxyethyl)-3,4-dimethylpiperidin-4-yl]phenol



C17 H27 N O2; Mol wt: 277.4053

ACTION – Agent for the prevention or treatment of pruritus reported to inhibit hind leg scratching behavior induced by s.c. injection of 5-methoxytryptamine in rats following s.c. administration. A representative compound from a series of 4-arylpiperidine derivatives.

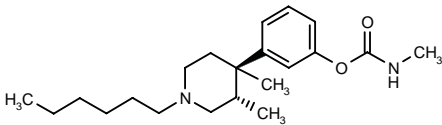
SOURCE – Pfizer.

REFERENCES

1. Gibson, S.P. and Tommasini, I. (Pfizer Inc.;Pfizer Ltd.) *4-Arylpiperidine derivs. for the treatment of pruritus.* EP 1072595, JP 2001019672.

299759

(±)-*trans*-*N*-Methylcarbamic acid 3-(1-hexyl-3,4-dimethylpiperidin-4-yl)phenyl ester



C21 H34 N2 O2; Mol wt: 346.5116

ACTION – Agent for the prevention or treatment of pruritus reported to inhibit hind leg scratching behavior induced by s.c. injection of 5-methoxytryptamine in rats following s.c. administration. A representative compound from a series of 4-arylpiperidine derivatives.

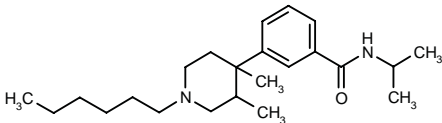
SOURCE – Pfizer.

REFERENCES

1. Armer, R.E. et al. (Pfizer Inc.;Pfizer Ltd.) *4-Arylpiperidine derivs. for the treatment of pruritus*. EP 1072594, JP 2000351765.

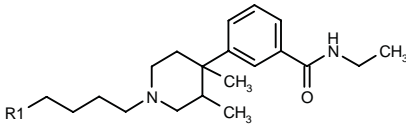
299762

3-(1-Hexyl-3,4-dimethylpiperidin-4-yl)-*N*-isopropylbenzamide



C23 H38 N2 O; Mol wt: 358.5662

ACTION – Agent for the prevention or treatment of diseases mediated by opiate receptors such as pruritus that exhibits affinity for opiate receptors such as mu, kappa and delta opioid receptors, as demonstrated in a binding assay selective for mu receptors in dog brain tissue by a K_i value of 4000 nM or less. Other exemplified compounds from this series of 4-arylpiperidine derivatives include the following:



Compound	R1	Formula
299764	Et	C ₂₂ H ₃₈ N ₂ O
299766	i-Pr	C ₂₃ H ₃₈ N ₂ O
299767	CH ₂ CN	C ₂₂ H ₃₃ N ₃ O

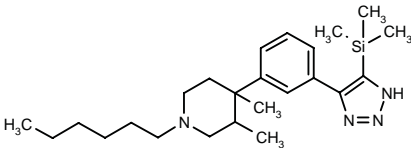
SOURCE – Pfizer.

REFERENCES

1. Armer, R.E. et al. (Pfizer Inc.;Pfizer Ltd.) *4-Arylpiperidine derivs. for the treatment of pruritus*. EP 1072592, JP 2000344746.

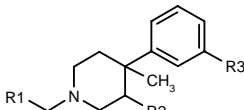
299768

1-Hexyl-3,4-dimethyl-4-[3-[5-(trimethylsilyl)-1*H*-1,2,3-triazol-4-yl]phenyl]piperidine



C24 H40 N4 Si; Mol wt: 412.6940

ACTION – Agent for the prevention or treatment of diseases mediated by opiate receptors such as pruritus which exhibits affinity for opiate receptors such as mu, kappa and delta opioid receptors, as demonstrated in a binding assay selective for mu receptors in dog brain tissue by a K_i value of 4000 nM or less. Other exemplified compounds from this series of 4-arylpiperidine derivatives include the following:



Compound	R1	R2	R3	Formula
299769	(CH ₂) ₃ CN	Me	1,2,3-triazol-4-yl	C ₂₀ H ₂₇ N ₅
299770	CH ₂ CH ₂ Ph	Me	1,2,3-triazol-4-yl	C ₂₄ H ₃₀ N ₄
299771	CH ₂ CH ₂ OPh	Me	1,2,3-triazol-4-yl	C ₂₄ H ₃₀ N ₄ O
299772	Pr	Me	1,2,3-triazol-4-yl	C ₁₉ H ₂₈ N ₄
299773	Ph	H	1,2,3-triazol-4-yl	C ₂₁ H ₂₄ N ₄
299774	C ₅ H ₁₁	H	1,2,3-triazol-4-yl	C ₂₀ H ₃₀ N ₄
299775	C ₅ H ₁₁	Me	5-tetrazolyl	C ₂₀ H ₃₁ N ₅
299776	C ₅ H ₁₁	Me	4-pyrazolyl	C ₂₂ H ₃₃ N ₃

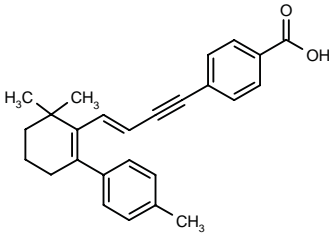
SOURCE – Pfizer.

REFERENCES

1. Armer, R.E. et al. (Pfizer Inc.;Pfizer Ltd.) *4-Arylpiperidine derivs. for the treatment of pruritus*. EP 1072601, JP 2001011072.

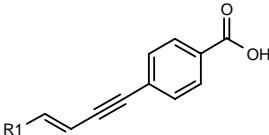
302637

4-[4-[6,6-Dimethyl-2-(4-methylphenyl)-1-cyclohexen-1-yl]-3(*E*)-buten-1-ynyl]benzoic acid



C26 H26 O2; Mol wt: 370.4894

ACTION – Selective retinoic acid receptor (RAR) antagonist with high binding affinity for RAR γ , RAR β and RAR α (K_d = 21, 6 and 148 nM, respectively) and able to inhibit TTNPB-induced transactivation at each RAR subtype, with selectivity for RAR γ over RAR α and RAR β (IC_{50} = 5, 210 and 22 nM, respectively). In the hairless mouse model of retinoid-induced topical irritation, compound applied topically reduced the severe cutaneous toxicity induced by TTNPB. Potentially useful for the treatment of mucocutaneous toxicity associated with systemic or topical retinoid treatment. Other related compounds are:



Compound	R1	Formula
302638	2-(4-Et-Ph)-6,6-(Me)2-1-cyclohexen-1-yl	C27H28O2
302639	2-(4-t-Bu-Ph)-6,6-(Me)2-1-cyclohexen-1-yl	C29H32O2
302640	6-(4-Me-Ph)-3,3-(Me)2--1,5-cyclohexadien-1-yl	C26H24O2

SOURCE – Allergan.

REFERENCES

1. Beard, R.L. et al. (Allergan, Inc.) *Aryl- and heteroaryl-cyclohexenyl substd. alkenes having retinoid agonist, antagonist or inverse agonist type biological activity*. EP 0970036, US 5760276, WO 9839284.

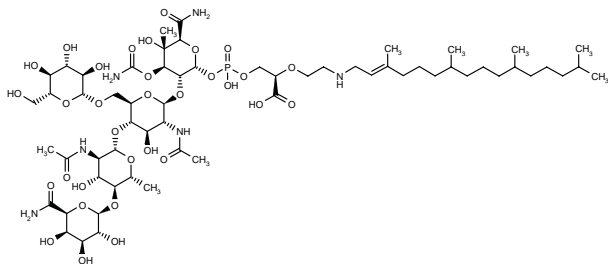
2. Beard, R.L. et al. *Phenylcyclohexene and phenylcyclohexadiene substituted compounds having retinoid antagonist activity*. Bioorg Med Chem Lett 2001, 11(6): 765.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

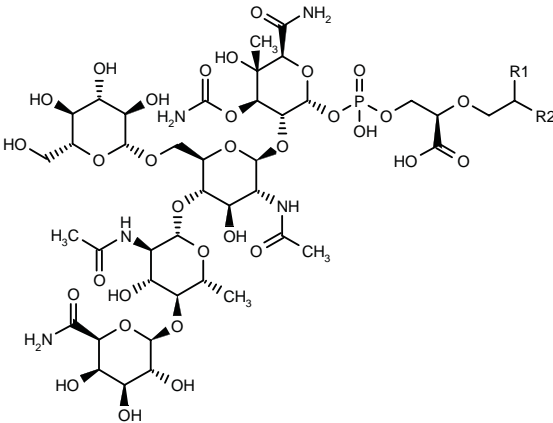
299314

O-(β -D-Galactopyranosyluronamido)-(1 \rightarrow 4)-*O*-(2-acetamido-2-deoxy- β -D-glucopyranosyl)-(1 \rightarrow 4)-*O*-[2-acetamido-2-deoxy-6-*O*-(β -D-glucopyranosyl)- β -D-glucopyranosyl]-(1 \rightarrow 2)-3-*O*-carbamoyl-1-*O*-[2(*R*)-carboxy-2-(3,7,11,15-tetramethyl-2-hexadecenyl-amino)ethoxy(hydroxy)phosphoryl]-4-*C*-methyl- α -D-glucopyranuronamide



C61 H107 N6 O32 P; Mol wt: 1467.5000

ACTION – Moenomycin A derivative with antibacterial activity, particularly against Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes* and *Enterococcus faecium*. The compound was reported to be effective against *S. pyogenes* A561 at 1.2 μ g/ml or less. Other exemplified compounds are:



Compound	R1	R2	Formula
299316	4-(C12H25)-PhNH	H	C ₅₉ H ₉₇ N ₆ O ₃₂ P
299318	CH(vinyl)C9H19	OH	C ₅₃ H ₉₀ N ₆ O ₃₃ P

SOURCE – Aventis Pharma.

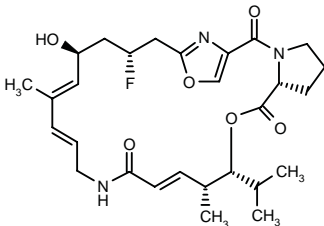
REFERENCES

1. Lampilas, M. and Vogel, S. (Aventis SA) *Moenomycin A derivs., their preparation, and use as antibacterial products*. EP 1069130.

299674

(3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,16*R*,26*aR*)-16-Fluoro-14-hydroxy-3-isopropyl-4,12-dimethyl-3,4,8,9,14,15,16,17,24,25,26-dodecahydro-7*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]dioxadiazacyclotetracosine-1,7,22-trione

16-Deoxo-16(*R*)-fluoropristinamycin IIB



C28 H38 F N3 O6; Mol wt: 531.6212

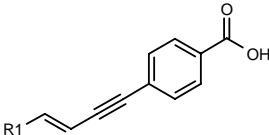
ACTION – Antibacterial agent, a compound from a series of group A streptogramin derivatives that exhibits potent activity both alone and in combination with a group B streptogramin derivative, displaying a broader spectrum of activity compared to the streptogramins and low toxicity.

SOURCE – Aventis Pharma.

REFERENCES

1. Achard, D. et al. (Aventis Pharma SA) *Streptogramin derivs., preparation and compsns. containing them*. FR 2795733, WO 0102427.

ACTION – Selective retinoic acid receptor (RAR) antagonist with high binding affinity for RAR γ , RAR β and RAR α (K_d = 21, 6 and 148 nM, respectively) and able to inhibit TTNPB-induced transactivation at each RAR subtype, with selectivity for RAR γ over RAR α and RAR β (IC_{50} = 5, 210 and 22 nM, respectively). In the hairless mouse model of retinoid-induced topical irritation, compound applied topically reduced the severe cutaneous toxicity induced by TTNPB. Potentially useful for the treatment of mucocutaneous toxicity associated with systemic or topical retinoid treatment. Other related compounds are:



Compound	R1	Formula
302638	2-(4-Et-Ph)-6,6-(Me)2-1-cyclohexen-1-yl	C27H28O2
302639	2-(4-t-Bu-Ph)-6,6-(Me)2-1-cyclohexen-1-yl	C29H32O2
302640	6-(4-Me-Ph)-3,3-(Me)2--1,5-cyclohexadien-1-yl	C26H24O2

SOURCE – Allergan.

REFERENCES

1. Beard, R.L. et al. (Allergan, Inc.) *Aryl- and heteroaryl-cyclohexenyl substd. alkenes having retinoid agonist, antagonist or inverse agonist type biological activity*. EP 0970036, US 5760276, WO 9839284.

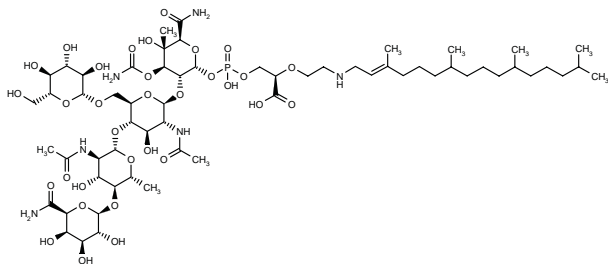
2. Beard, R.L. et al. *Phenylcyclohexene and phenylcyclohexadiene substituted compounds having retinoid antagonist activity*. Bioorg Med Chem Lett 2001, 11(6): 765.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

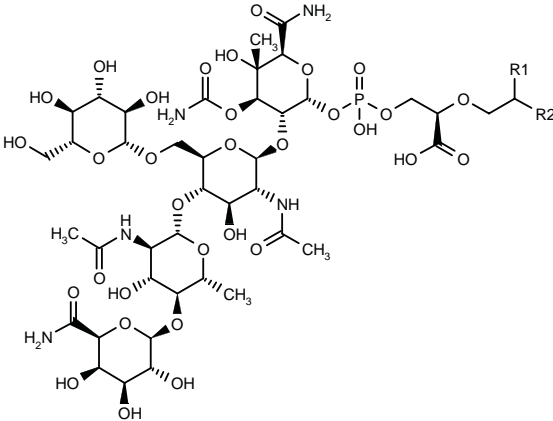
299314

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SOURCE – Aventis Pharma.

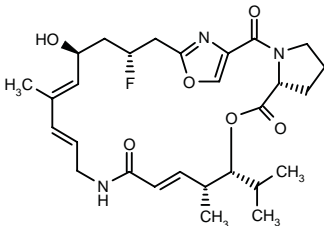
REFERENCES

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299674

(3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,16*R*,26*aR*)-16-Fluoro-14-hydroxy-3-isopropyl-4,12-dimethyl-3,4,8,9,14,15,16,17,24,25,26-dodecahydro-7*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]dioxadiazacyclotetracosine-1,7,22-trione

16-Deoxo-16(*R*)-fluoropristinamycin IIB



C28 H38 F N3 O6; Mol wt: 531.6212

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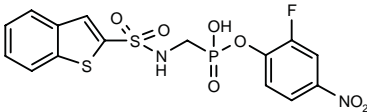
SOURCE – Aventis Pharma.

REFERENCES

1. Achard, D. et al. (Aventis Pharma SA) *Streptogramin derivs., preparation and compsns. containing them*. FR 2795733, WO 0102427.

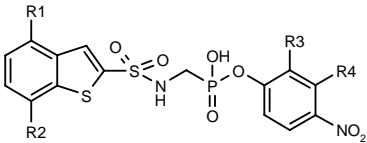
300181

(2-Benzothieryl)sulfonamidomethylphosphonic acid 2-fluoro-4-nitrophenyl monoester

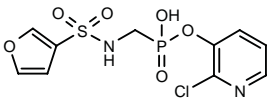


C15 H12 F N2 O7 P S2; Mol wt: 446.3708

ACTION – β -Lactamase inhibitor giving an IC₅₀ value of 0.1 μ M against class C β -lactamase (P99). In addition, compound was shown to potentiate the activity of β -lactam antibiotics against *Enterobacter cloacae* ATCC23355 (class C), *Haemophilus influenzae* ATCC43163 (class A) and *Staphylococcus aureus* MGH:MA50848 (class A) by 8-, 32- and 2-fold, respectively, at 10 μ g/ml; synergistic effects with β -lactam antibiotics were also observed in highly resistant microorganisms such as *E. cloacae* (derepressed), *Stenotrophomas maltophilia* ATCC12968 and *Pseudomonas aeruginosa* ATCC 98043010 at 10 μ g/ml (5-, 5- and 8-fold potentiation, respectively). Other exemplified compounds from this series of sulfonamidomethyl phosphonate derivatives include the following:



Compound	R1	R2	R3	R4	Formula
300182	H	H	H	H	C ₁₅ H ₁₃ N ₂ O ₇ PS ₂
300183	Cl	Cl	F	H	C ₁₅ H ₁₀ Cl ₂ FN ₂ O ₇ PS ₂
300184	Cl	Cl	H	CF ₃	C ₁₆ H ₁₀ Cl ₂ F ₃ N ₂ O ₇ PS ₂
300185	Cl	Cl	H	CN	C ₁₆ H ₁₀ Cl ₂ N ₃ O ₇ PS ₂
300186	Cl	Cl	H	H	C ₁₅ H ₁₁ Cl ₂ N ₂ O ₇ PS ₂
300187	Cl	H	H	H	C ₁₅ H ₁₂ ClN ₂ O ₇ PS ₂



300188: C10 H10 Cl N2 O6 P S

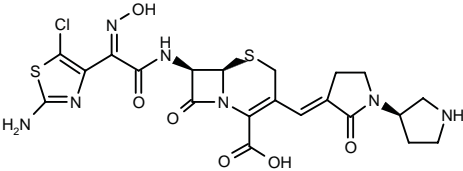
SOURCE – MethylGene.

REFERENCES

1. Besterman, J.M. et al. (MethylGene Inc.) Sulfonamidomethyl phosphonate inhibitors of β -lactamase. WO 0102411.

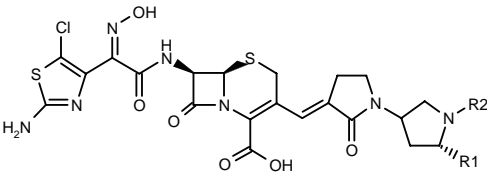
300197

(6*R*,7*R*)-7-[(*Z*)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(*E*)-[(3'*R*)-2-oxo-1,3'-bipyrrolidin-3-ylidenemethyl]-3-cephem-4-carboxylic acid



C21 H22 Cl N7 O6 S2; Mol wt: 568.0328

ACTION – Antibacterial agent for the treatment and prophylaxis of infectious diseases, especially infectious diseases caused by methicillin-resistant *Staphylococcus aureus* (MRSA). *In vitro*, compound gave MIC values of 0.5, 1, 1, 1, 1, 0.5, 1, 0.12 and < 0.1 μ g/ml, respectively, against MRSA strains 743, 270A, 42080 and H19982, *Klebsiella pneumoniae* strains B7368 (SHV-2) and 26768 WU (SHV-5), *Enterobacter cloacae* 908R, *Citrobacter freundii* 1982 and *Proteus vulgaris* 1028. Other specifically claimed compounds from this series of cephalosporin derivatives bearing a substituted thiazole ring are:



Compound	R1	R2	Isomer	Formula
300198	H	5-Me-2-oxo- -1,3-dioxol-4-yl-CH2OCO	3R	C ₂₇ H ₂₈ ClN ₇ O ₁₁ S ₂
300199	CH2OH	H	3R	C ₂₂ H ₂₄ ClN ₇ O ₇ S ₂
300200	CH2OH	5-Me-2-oxo- -1,3-dioxol-4-yl-CH2OCO	3R	C ₂₈ H ₃₀ ClN ₇ O ₁₂ S ₂
300201	H	H	3S	C ₂₁ H ₂₂ ClN ₇ O ₆ S ₂
300202	H	5-Me-2-oxo- -1,3-dioxol-4-yl-CH2OCO	3S	C ₂₇ H ₂₈ ClN ₇ O ₁₁ S ₂

SOURCE – Roche.

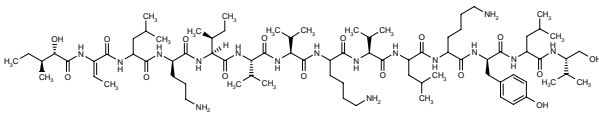
REFERENCES

1. Angehrn, P. et al. (F. Hoffmann-La Roche AG) Vinylpyrrolidinone derivs. with subst. thiazole ring. WO 0104127.

BOGOROL A

299494

N-[2-[2(*S*)-Hydroxy-3(*S*)-methylpentanamido]-2(*E*)-butenoyl]-leucyl-D-ornithyl-L-isoleucyl-L-valyl-L-valyl-L-lysyl-L-valyl-leucyl-L-tyrosyl-leucyl-L-valinol



C80 H142 N16 O16; Mol wt: 1584.0980

ACTION – Peptide antibiotic produced in cultures of a marine *Bacillus* sp. collected in Papua New Guinea and tentatively identified as *Bacillus laterosporus*. Compound showed good antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci (MIC = 2 and 10 µg/ml, respectively) and moderate activity against *Escherichia coli* (MIC = 35 µg/ml). Considered an attractive lead structure for further chemical optimization in order to synthesize novel potent antibacterial agents.

SOURCES – University of Alberta, Edmonton, AB (CA); University of British Columbia, Vancouver, BC (CA); SeaTek.

REFERENCES

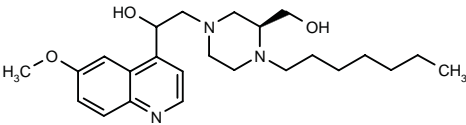
1. Barsby, T. et al. *Bogorol A produced in culture by a marine Bacillus sp. reveals a novel template for cationic peptide antibiotics*. Org Lett 2001, 3(3): 437.

2. Barsby, T. et al. *Bogorols: A new family of cationic peptide antibiotics produced in cultured by a marine Bacillus sp.* 17th Am Peptide Symp (June 9-14, San Diego) 2001, Abst P462.

ANTIBACTERIAL DRUGS

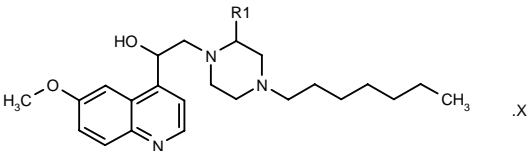
299169

2-[4-Heptyl-3(S)-(hydroxymethyl)piperazin-1-yl]-1-(6-methoxyquinolin-4-yl)ethanol



C24 H37 N3 O3; Mol wt: 415.5743

ACTION – Quinoline antibacterial agent with MIC values of 1 µg/ml or less against *Staphylococcus aureus* Oxford, *S. aureus* WCUH29, *S. aureus* Carter 37, *Enterococcus faecalis* I, *Moraxella catarrhalis* Ravasio and *Streptococcus pneumoniae* R6. Other exemplified compounds are:



Compound	R1	X	Formula
299170	(S)-CH2CH2OH	dioxalate	C ₂₅ H ₃₉ N ₃ O ₃ ·2C ₂ H ₂ O ₄
299171	H		C ₂₃ H ₃₆ N ₃ O ₂
299173	(R)-CH2CH2OH	oxalate	C ₂₅ H ₃₉ N ₃ O ₃ ·C ₂ H ₂ O ₄

SOURCE – GlaxoSmithKline.

REFERENCES

1. Davies, D.T. et al. (SmithKline Beecham plc) *Quinoline derivs. as antibacterials*. WO 0078748.

299298

L-Arginyl-L-arginyl-L-leucyl-L-cysteinyl-L-arginyl-L-isoleucyl-L-valyl-L-tryptophyl-L-valyl-L-isoleucyl-L-arginyl-L-valyl-L-cysteinyl-L-arginyl-L-arginine

C86 H154 N34 O16 S2; Mol wt: 1984.5170

ACTION – Antimicrobial peptide, a derivative of bactenecin proven active against Gram-positive bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Corynebacterium xerosis*, *Streptococcus pyogenes*, *Streptococcus mitis* and *Streptococcus pneumoniae* (MIC = 0.25-8 µg/ml), and Gram-negative bacteria such as *Escherichia coli* UB1005, *Pseudomonas aeruginosa* and *Salmonella typhimurium* (MIC = 2 µg/ml).

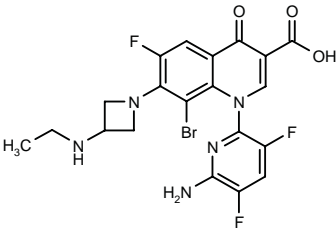
SOURCE – University of British Columbia, Vancouver, BC (CA).

REFERENCES

1. Hancock, R.E.W. and Wu, M. (University of British Columbia) *Antimicrobial catinoic peptide derivs. of bactenecin*. US 6172185.

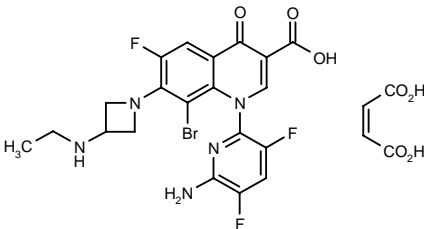
299706

1-(6-Amino-3,5-difluoropyridin-2-yl)-8-bromo-7-[3-(ethy-amino)azetidin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C20 H17 Br F3 N5 O3; Mol wt: 512.2843

ACTION – Quinolone antibacterial agent active against Gram-positive and Gram-negative strains, as demonstrated by MIC values of 0.013, 0.013, 0.025, 0.39, 0.025, 0.025, 0.05 and 0.78 µg/ml, respectively, against *Staphylococcus aureus* 209P, methicillin-resistant *S. aureus* W200, *Staphylococcus epidermidis* IFO12293, *Enterococcus faecalis* IFO12580, *Bacillus subtilis* ATCC6633, *Escherichia coli* NIHJ-JC2, *Klebsiella pneumoniae* KC-1 and *Pseudomonas aeruginosa* IFO3445; in addition, compound was found to be active against ciprofloxacin- or levofloxacin-resistant strains. No phototoxicity was observed in mice following administration of 40 mg/kg i.v. Half-life in dogs following p.o. administration was 3.8 h. Also exemplified is the following salt:



299707: C20 H17 Br F3 N5 O3 . C4 H4 O4

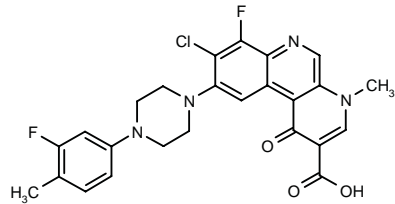
SOURCE – Wakunaga.

REFERENCES

1. Yazaki, A. et al. (Wakunaga Pharmaceutical Co., Ltd.) *Quinolinecarboxylic acid deriv. or salts thereof*. WO 0102390.

299911

8-Chloro-7-fluoro-9-[4-(3-fluoro-4-methylphenyl)piperazin-1-yl]-4-methyl-1-oxo-1,4-dihydrobenzo[*f*]-1,7-naphthyridine-2-carboxylic acid



C25 H21 Cl F2 N4 O3; Mol wt: 498.9149

ACTION – Antibacterial benzo[*f*]naphthyridine derivative with activity against Gram-positive organisms and particularly against quinolone-resistant bacteria. It was reported to be active *in vitro* against *Staphylococcus aureus* IP8203 and the quinolone-resistant strain *S. aureus* LF11C128B, and *in vivo* against *S. aureus* TCC 25923 infection.

SOURCE – Aventis Pharma.

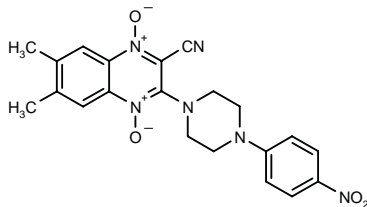
REFERENCES

1. Desconclois, J.-F. et al. (Aventis Pharma SA) *Novel benzo[*f*]naphthyridine, preparation and compns. containing them*. FR 2795729, WO 0102396.

ANTIMYCOBACTERIAL AGENTS

302580

6,7-Dimethyl-3-[4-(4-nitrophenyl)piperazin-1-yl]quinoxaline-2-carbonitrile 1,4-dioxide



C21 H20 N6 O4; Mol wt: 420.4270

ACTION – Antibacterial agent active against *Mycobacterium tuberculosis* (MIC > 0.2 µM), with low cytotoxicity and a high selectivity index (> 125). Compound is currently being tested in *in vivo* models of tuberculosis infection.

SOURCES – Universidad Nacional Mayor San Marcos, Lima (PE); Universidad de Navarra, Pamplona (ES).

REFERENCES

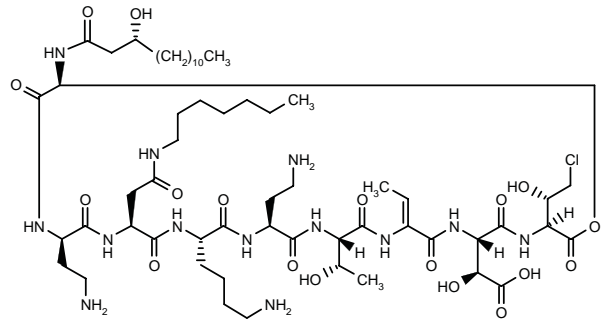
1. Ortega, M.A. et al. *Antimycobacterial activity of new quinoxaline-2-carbonitrile and quinoxaline-2-carbonitrile 1,4-di-N-oxide derivatives*. Pharmazie 2001, 56(3): 205.
2. Ortega, M.A. et al. *New quinoxalinecarbonitrile 1,4-di-N-oxide derivatives as hypoxic-cytotoxic agents*. Eur J Med Chem 2000, 35(1): 21.

ANTIFUNGAL AGENTS

300379

N-[3(*R*)-Hydroxytetradecanoyl]-L-seryl-D-2,4-diaminobutryl-*N*⁴-heptyl-L-asparaginyll-L-lysyl-L-2,4-diaminobutryl-L-allothreonyl-(*Z*)-2,3-didehydro-2-aminobutryl-3(*S*)-hydroxy-L-aspartyl-4-chloro-L-threonine C-1.9-*O*-3.1-lactone

2(*S*)-[(3*S*,6*S*,9(*Z*),12*S*,15*S*,18*S*,21*S*,24*R*,27*S*)-18-(4-Aminobutyl)-15,24-bis(2-aminoethyl)-3-[2-chloro-1(*S*)-hydroxyethyl]-9-ethylidene-21-[2-(heptylamino)-2-oxoethyl]-12-[1(*S*)-hydroxyethyl]-27-[3(*R*)-hydroxytetradecanamido]-2,5,8,11,14,17,20,23,26-nonaoxo-1-oxa-4,7,10,13,16,19,22,25-octaazacyclooctacos-6-yl]-2-hydroxyacetic acid



C58 H102 Cl N13 O18; Mol wt: 1304.9700

ACTION – Antifungal agent that exhibits an MIC value of 20 µg/ml against *Candida albicans*. A representative compound from a series of pseudomycin amide and ester analogues.

SOURCE – Lilly.

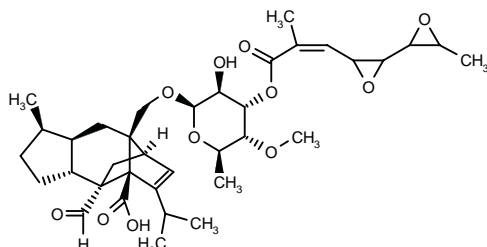
REFERENCES

1. Chen, S.H. et al. (Eli Lilly and Company) *Pseudomycin amide and ester analogs*. WO 0105817.

FR-231956

299323

[1*R*-(1 α ,3 α ,4 α ,4 β ,7 β ,7 α ,8 α)]-8a-[6-Deoxy-4-*O*-methyl-3-*O*-[2-methyl-3-(3'-methyl-2,2'-bioxiran-3-yl)-2(*Z*)-propenoyl]- β -D-altropyranosyloxymethyl]-4-formyl-3-isopropyl-7-methyl-1,3a,4,4a,5,6,7,7a,8,8a-decahydro-1,4-methano-*s*-indacene-3a-carboxylic acid



C36 H50 O11; Mol wt: 658.7800

ACTION – Antimicrobial sordarin derivative isolated from the fermentation of the fungus *Sordaria araneosa* ATCC 36386. This compound exhibited excellent antifungal activity and a broad spectrum of activity, as demonstrated against *Candida albicans* FP629 and *Cryptococcus neoformans* YC203, with minimal effective concentrations of 0.05 and 0.03 μ g/ml, respectively.

SOURCE – Fujisawa.

REFERENCES

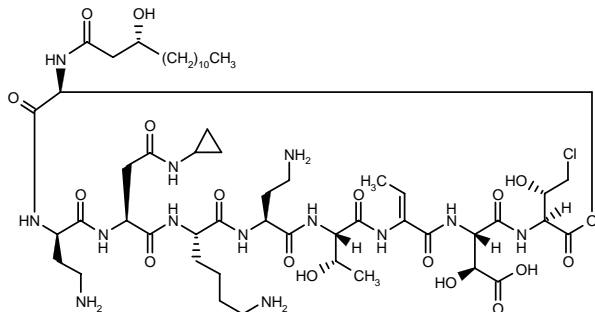
1. Hori, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel sordarin deriv. as a therapeutic antimicrobial agent*. WO 0100639.

LY-448212

302641

N-3(*R*)-(Hydroxytetradecanoyl)-L-seryl-D-2,4-diaminobutyl-3-(cyclopropylcarbamoyl)-L-alanyl-L-lysyl-L-2,4-diaminobutyl-L-allothreonyl-(*Z*)-2,3-didehydro-2-aminobutyl-3(*S*)-hydroxy-L-aspartyl-4-chloro-L-threonine C-1.9-*O*-3.1-lactone

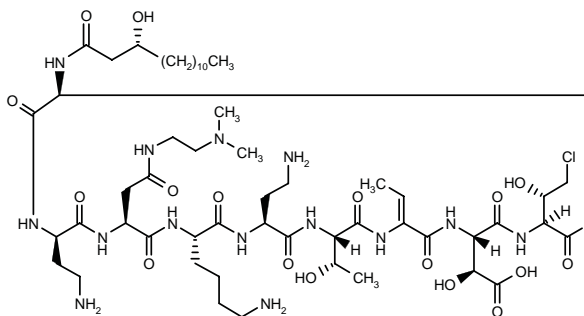
3-(*N*-Cyclopropyl-L-asparagine)pseudomycin B



C54 H92 Cl N13 O18; Mol wt: 1246.8470

ACTION – Antifungal agent active against *Candida albicans* and *Cryptococcus neoformans* (MIC = 0.156 and < 0.01 μ g/ml, respectively), with weak activity against *Aspergillus fumigatus* (MIC = 20 μ g/ml). *In vivo*, it showed good efficacy against cryptococcosis (ED₅₀ = 2.5-2.9 mg/kg i.p.) and candidiasis (ED₅₀ < 5 mg/kg i.p.) in mice, with no signs of toxicity at up to 75 mg/kg i.v. Two-week

toxicity studies with compound at 50 and 75 mg/kg i.v. demonstrated no systemic or vein toxicity. When compared with the parent compound pseudomycin, this derivative showed improved antifungal activity and safety. Another 3-amido pseudomycin B analogue is:



LY-448731 [302643]: C55 H97 Cl N14 O18

SOURCE – Lilly.

REFERENCES

1. Chen, S.H. et al. (Eli Lilly and Company) *Pseudomycin amide and ester analogs*. WO 0105817.

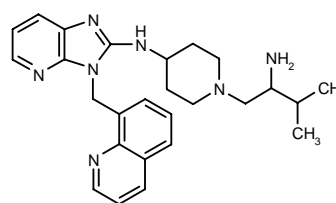
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3. Zhang, Y.-Z. et al. *Synthesis and antifungal activities of novel 3-amido bearing pseudomycin analogues*. Bioorg Med Chem Lett 2001, 11(7): 903.

ANTIVIRAL DRUGS

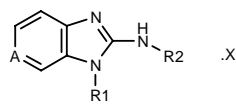
299442

N-[1-(2-Amino-3-methylbutyl)piperidin-4-yl]-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amine



C26 H33 N7; Mol wt: 443.5957

ACTION – Antiviral agent active against respiratory syncytial virus (RSV), as demonstrated *in vitro* by an IC₅₀ value of 0.0004 μ M against RSV in infected HeLa cells, with low cytotoxicity (CC₅₀ > 10.05 μ M in uninfected cells; selectivity index [SI] > 25,119). Other exemplified compounds from this series of benzimidazole and imidazopyridine derivatives include the following:



Compound	R1	R2	A	X	Formula
299443	8-quinolyl-CH2-CH2OCH(OEt)	1-[i-PrCH(NH2)CH2]-4-Pip	CH		C ₃₁ H ₄₂ N ₆ O ₂
299444	2-Br-5,6,7,8-tetrahydro-8-quinolyl	1-[i-PrCH(NH2)CH2]-4-Pip	CH	.3HCl .3H2O	C ₂₆ H ₃₅ BrN ₆ .3HCl.3H ₂ O
299447	8-quinolyl-CH2	1-[i-PrCH(NH2)CH2]-4-Pip	N	.3HCl .2H2O	C ₂₆ H ₃₃ N ₇ .3HCl.2H ₂ O
299449	8-quinolyl-CH2	CH2CH2NH-CH2CH2NH2	CH		C ₂₁ H ₂₄ N ₆

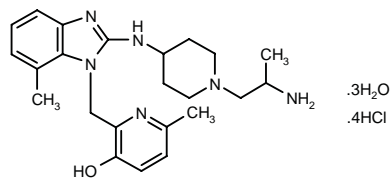
SOURCE – Janssen.

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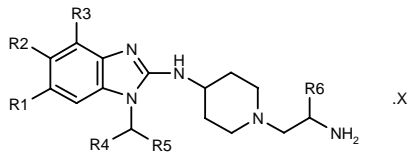
299450

2-[2-[1-(2-Aminopropyl)piperidin-4-ylamino]-7-methyl-1 *H*-benzimidazol-1-ylmethyl]-6-methylpyridin-3-ol tetrahydrochloride trihydrate



C23 H32 N6 O . 4 HCl . 3 H2 O; Mol wt: 608.4348

ACTION – Antiviral agent active against respiratory syncytial virus (RSV), as demonstrated *in vitro* by an IC₅₀ value of 0.00032 μM against RSV in infected HeLa cells, with low cytotoxicity (CC₅₀ = 63.85 μM in uninfected cells; selectivity index [SI] = 199,526). Other exemplified compounds from this series of benzimidazole and imidazopyridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
299452	H	H	Me	3-OH-6-Me-2-Pyr	H	i-Pr	.4HCl .H2O	C ₂₅ H ₃₆ N ₆ O .4ClH.H ₂ O
299453	H	Cl	H	1,4-(Me)2-5-imidazolyl	H	i-Pr	H2O	C ₂₃ H ₃₄ ClN ₇ .H ₂ O
299455	Me	H	H	6-Me-2-Pyr	H	i-Pr		C ₂₅ H ₃₆ N ₆
299456	H	H	H	3-(HOCH2CH2O)-6-Me-2-Pyr	H	H	.3HCl .H2O	C ₂₃ H ₃₂ N ₆ O ₂ .3HCl.H ₂ O
299458	H	H	H	6-Me-2-Pyr	Me	H		C ₂₂ H ₃₀ N ₆

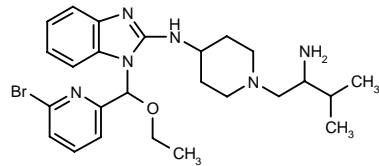
SOURCE – Janssen.

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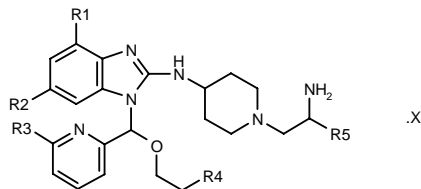
299460

N-[1-(2-Amino-3-methylbutyl)piperidin-4-yl]-1-[1-(6-bromopyridin-2-yl)-1-ethoxymethyl]-1 *H*-benzimidazol-2-amine



C25 H35 Br N6 O; Mol wt: 515.4965

ACTION – Antiviral agent active against respiratory syncytial virus (RSV), as demonstrated *in vitro* by an IC₅₀ value of 0.0006 μM against RSV in infected HeLa cells, with low cytotoxicity (CC₅₀ = 37.86 μM in uninfected cells; selectivity index [SI] = 63,096). Other exemplified compounds from this series of benzimidazole and imidazopyridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
299462	Me	H	Br	H	i-Pr	H2O	C ₂₆ H ₃₇ BrN ₆ O.H ₂ O
299464	Me	Cl	Me	OMe	i-Pr	.3HCl .3H2O	C ₂₈ H ₄₁ ClN ₆ O ₂ .3HCl.3H ₂ O
299466	H	H	Me	H	i-Pr	H2O	C ₂₆ H ₃₈ N ₆ O.H ₂ O
299468	H	H	Me	OH	H	H2O	C ₂₃ H ₃₂ N ₆ O ₂ .H ₂ O

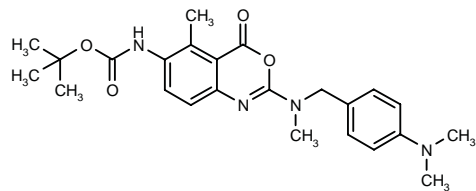
SOURCE – Janssen.

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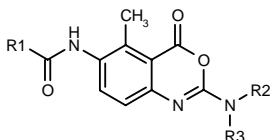
300138

N-[2-[*N*-[4-(Dimethylamino)benzyl]-*N*-methylamino]-5-methyl-4-oxo-4*H*-3,1-benzoxazin-6-yl]carbamic acid *tert*-butyl ester



C24 H30 N4 O4; Mol wt: 438.5250

ACTION – Antiviral agent active against herpes simplex virus (HSV) that acts by inhibiting HSV protease (assemblin). This compound was found to inhibit recombinant HSV-1 protease ($IC_{50} = 1.3 \mu M$) while having no inhibitory effect on human leukocyte elastase and bovine chymotrypsin at $50 \mu M$. In addition, compound exhibited potent antiviral activity against HSV-1 in Vero cells, giving an EC_{50} of $0.05 \mu M$. Other exemplified 2-aminobenzoxazinones include the following:



Compound	R1	R2	R3	Formula
300140	t-BuO	Me	CH ₂ Ph	C ₂₂ H ₂₅ N ₃ O ₄
300141	Ph	Me	CH ₂ Ph	C ₂₄ H ₂₁ N ₃ O ₃
300142	t-BuO	Me	4-MeO-PhCH ₂	C ₂₃ H ₂₇ N ₃ O ₅
300143	t-BuO	-CH ₂ CH ₂ N(SO ₂ Ph)CH ₂ CH ₂ -		C ₂₄ H ₂₈ N ₄ O ₆ S

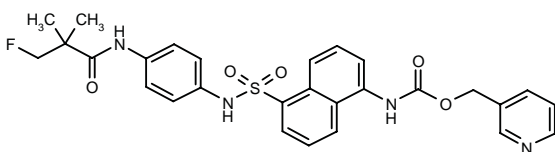
SOURCES – Asahi Kasei; Pharmacia.

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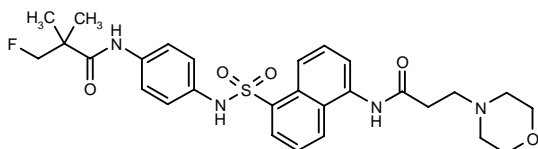
300576

N-[5-[*N*-[4-(3-Fluoro-2,2-dimethylpropionamido)phenyl]-sulfamoyl]naphthalen-1-yl]carbamic acid 3-pyridinylmethyl ester



C₂₈ H₂₇ F N₄ O₅ S; Mol wt: 550.6083

ACTION – Antiviral agent for the treatment of infections caused by cytomegaloviruses, with potent activity against human cytomegalovirus (HCMV) in infected human embryonal lung fibroblasts (HELFI; $EC_{50} = 0.049 \mu M$). Another compound from this series of naphthylsulfonamides is:



300577: C₂₈ H₃₃ F N₄ O₅ S

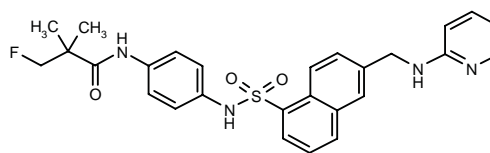
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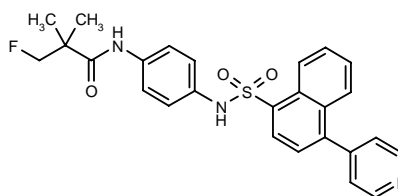
300578

3-Fluoro-2,2-dimethyl-*N*-[4-[6-(2-pyridinylamino-methyl)naphthalen-1-ylsulfonamido]phenyl]propionamide



C₂₇ H₂₇ F N₄ O₃ S; Mol wt: 506.5993

ACTION – Antiviral agent for the treatment of infections caused by cytomegaloviruses, with potent activity against human cytomegalovirus (HCMV) in infected human embryonal lung fibroblasts (HELFI; $EC_{50} = 0.049 \mu M$) and low cytotoxicity in uninfected cells ($CC_{50} > 31 \mu M$). Another compound from this series of naphthylsulfonamides is:



300579: C₂₆ H₂₄ F N₃ O₃ S

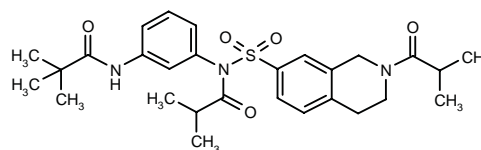
SOURCE – Bayer.

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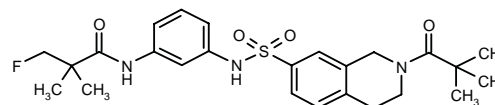
300580

2,2-Dimethyl-*N*-[3-[*N*-(2-methylpropionyl)-*N*-[2-(2-methylpropionyl)-1,2,3,4-tetrahydroisoquinolin-7-yl-sulfonyl]amino]phenyl]propionamide



C₂₈ H₃₇ N₃ O₅ S; Mol wt: 527.6823

ACTION – Antiviral agent for the treatment of infections caused by cytomegaloviruses, with potent activity against human cytomegalovirus (HCMV) in infected human embryonal lung fibroblasts (HELFI; $EC_{50} = 0.49 \mu M$) and low cytotoxicity in uninfected cells ($CC_{50} = 31 \mu M$). Another compound from this series of tetrahydroisoquinolinesulfonamides is:



300581: C₂₅ H₃₂ F N₃ O₄ S

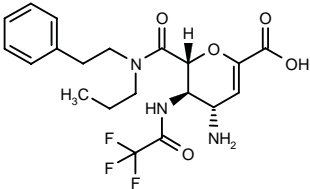
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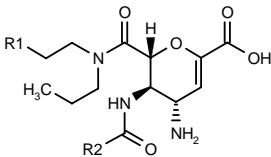
301470

(4*S*,5*R*,6*R*)-4-Amino-6-[*N*-(2-phenylethyl)-*N*-propylcarbamoyl]-5-(trifluoroacetamido)-5,6-dihydro-4*H*-pyran-2-carboxylic acid



C20 H24 F3 N3 O5; Mol wt: 443.4196

ACTION – Influenza A sialidase (neuraminidase) inhibitor with improved selectivity over influenza B enzyme compared with zanamivir (IC₅₀ = 0.003 and 0.1 μM, respectively, for compound vs. 0.002 and 0.04 μM, respectively, for zanamivir). Despite its high enzymatic selectivity, in the plaque reduction assay compound was only 14-fold more potent against influenza A than influenza B virus (IC₅₀ = 0.004 and 0.056 μg/ml, respectively). Other 4-amino-4*H*-pyran-2-carboxylic acid-6-carboxamides include the following:



Compound	R1	R2	Formula
301468	Me	CF3	C ₁₅ H ₂₂ F ₃ N ₃ O ₅
301469	Ph	Et	C ₂₁ H ₂₉ N ₃ O ₅
301471	Me	Et	C ₁₆ H ₂₇ N ₃ O ₅

SOURCE – Biota Scientific Management.

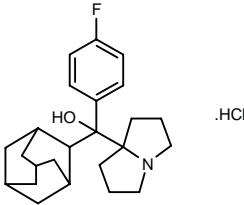
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302624

1-(2-Adamantyl)-1-(4-fluorophenyl)-1-(1,5-perhydropyrrolizin-7a-yl)methanol hydrochloride



C24 H32 F N O . HCl ; Mol wt: 405.9817

ACTION – Antiviral agent active against influenza A virus, a triperiden-based compound with an improved *in vitro* antiviral activity and safety profile and reduced *in vivo* neurotoxicity after i.p. administration to mice.

SOURCE – Sanwa.

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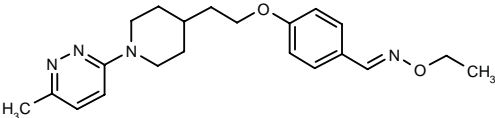
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BTA-188

299109

4-[2-[1-(6-Methylpyridazin-3-yl)piperidin-4-yl]ethoxy]-benzaldehyde (*E*)-*O*-ethyloxime



C21 H28 N4 O2; Mol wt: 368.4782

ACTION – Antiviral agent, a picornavirus capsid-binding inhibitor especially active against a wide range of human rhinovirus (HRV) strains. Compound inhibited 87 of 100 HRV serotypes with a median EC₅₀ of 0.01 μg/ml and 40 recent clinical isolates with a median EC₅₀ of 0.004 μg/ml; for comparison, pleconaril inhibited 81 of 100 serotypes and 33 of 44 clinical isolates at 1 μg/ml. Compound was not virucidal for RV-2 and not cytotoxic at up to 2 μg/ml. It also inhibited enteroviruses including echoviruses, polioviruses and coxsackie A and B viruses (EC₅₀ > 200 nM). Pharmacokinetic experiments in rats and dogs demonstrated good oral absorption, with an oral bioavailability of 62-64% in rats and 21-28% in dogs. Moreover, mean concentrations in nasal epithelium in dogs were 25-fold the plasma concentrations and exceeded the median EC₉₀ for antirhinoviral activity.

SOURCE – Biota Scientific Management.

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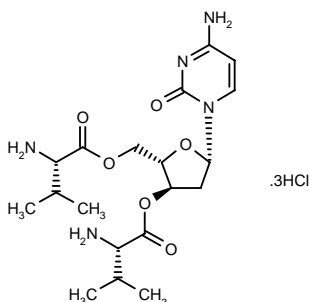
DI-VAL-L-dC

302168

1-[3,5-Di-*O*-(*L*-valyl)-2-deoxy- β -*L*-ribofuranosyl]cytosine trihydrochloride

3',5'-Di-*O*-(*L*-valyl)- β -*L*-2'-deoxycytidine trihydrochloride

L-Valine 3',5'-diester with 4-amino-1-(2-deoxy- β -*L*-erythro-pentofuranosyl)-2(1*H*)-pyrimidinone trihydrochloride



C19 H31 N5 O6 . 3HCl; Mol wt: 534.8656

ACTION – Prodrug of β -*L*-dC*, a potent and selective inhibitor of human hepatitis B virus (HBV) replication, with improved oral bioavailability and stability. Pharmacokinetic studies in cynomolgus monkeys demonstrated that the prodrug given at a dose of 10 mg/kg p.o. in [3 H]-labeled form was rapidly and completely converted to β -*L*-dC. Peak plasma concentrations and AUC of β -*L*-dC reached after administration of the prodrug were significantly greater than after an equivalent dose of β -*L*-dC. Cellular levels of the triphosphate form of β -*L*-dC reached up to 100 times the EC₉₀ for HBV, with a half-life of 15 h. Selected for further studies as an anti-HBV agent.

SOURCES – CNRS; Université Montpellier II, Montpellier (FR); Novirio.

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*See **NV-02C** Drug Data Rep 2000, 022(07): 0626.

DOCUSATE SODIUM⁺

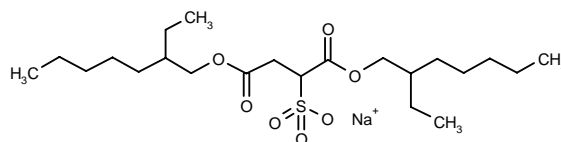
Product Update

120922

Sulfobutanedioic acid 1,4-bis(2-ethylhexyl) ester sodium salt

Sulfosuccinic acid 1,4-bis(2-ethylhexyl) ester sodium salt

DSS
MTCH-24
ZorexTM



C22 H41 Na O7 S; Mol wt: 472.6149

ACTION – Antiviral agent, a sulfate surfactant that inactivates viral pathogens by disrupting the viral envelope and/or denaturing proteins. It was active against both wild-type and drug-resistant strains of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2; EC₉₀₋₁₀₀ ~ 0.005% [w/v]). Pretreatment of cells with compound produced a 45% decrease in infectivity even after several washings, and 30% plaque reduction was seen when drug was added to infected cells. Potentially useful as a topical microbicide for preventing sexually transmitted diseases.

SOURCES – Immune Network; Meditech.

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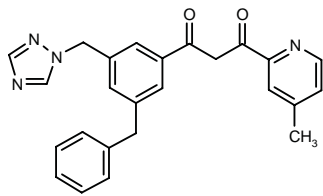
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⁺Drug Data Rep 1986, 008(11): 1083.

AIDS MEDICINES

299322

1-[3-Benzyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-3-(4-methylpyridin-2-yl)propane-1,3-dione



C25 H22 N4 O2; Mol wt: 410.4748

ACTION – A representative compound from a series of 1-(aromatic or heteroaromatic substituted)-3-(heteroaromatic substituted)-1,3-propanediones that inhibit the HIV integrase enzyme and are thus useful for the treatment or prevention of AIDS. Representative compounds are reported to exhibit IC₉₅ values of 0.01-50 μM for inhibition of acute HIV infection in T-lymphoid cells.

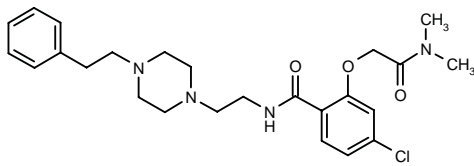
SOURCES – Merck & Co.; Tularik.

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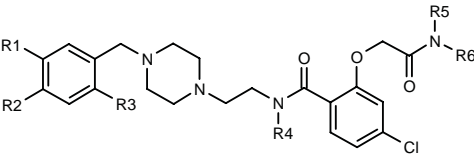
299847

4-Chloro-2-[2-(dimethylamino)-2-oxoethoxy]-*N*-[2-[4-(2-phenylethyl)piperazin-1-yl]ethyl]benzamide



C25 H33 Cl N4 O3; Mol wt: 473.0137

ACTION – Modulator of the chemokine receptors CCR1 and/or CCR3 that may be useful for the treatment of autoimmune, inflammatory, proliferative and hyperproliferative disorders, as well as immunologically mediated diseases such as transplant rejection or AIDS. Other specifically claimed piperazine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
299848	Cl	Cl	H	H	-(CH2)4-		C ₂₆ H ₃₁ Cl ₃ N ₄ O ₃
299849	Cl	Cl	H	Me	Me	Me	C ₂₅ H ₃₁ Cl ₃ N ₄ O ₃
299850	Cl	Cl	H	H	-CH2CH(CH2OH)(CH2)3-		C ₂₈ H ₃₅ Cl ₃ N ₄ O ₄
299851	Cl	Cl	H	H	1-(CH2OH)-1-cyclopentyl	H	C ₂₈ H ₃₅ Cl ₃ N ₄ O ₄
299852	Cl	Cl	H	H	-CH2CH2NHCH2CH2-		C ₂₆ H ₃₂ Cl ₃ N ₅ O ₃
299853	Cl	H	H	H	Me	Me	C ₂₄ H ₃₀ Cl ₃ N ₄ O ₃
299854	F	F	F	H	Me	Me	C ₂₄ H ₂₈ ClF ₃ N ₄ O ₃

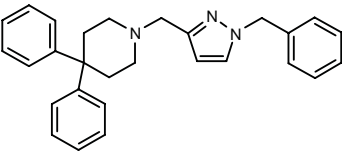
SOURCE – AstraZeneca.

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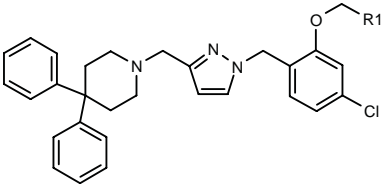
300271

1-(1-Benzyl-1*H*-pyrazol-3-ylmethyl)-4,4-diphenylpiperidine

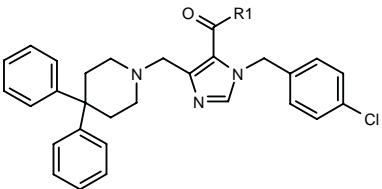


C28 H29 N3; Mol wt: 407.5581

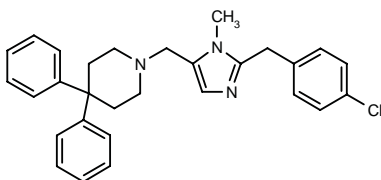
ACTION – Agent for the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases, transplant rejection and AIDS, particularly chronic obstructive pulmonary disease, rheumatoid arthritis and inflammation, a chemokine CCR1 and/or CCR3 receptor modulator. Other specifically claimed compounds from this series of diphenyl-piperidine derivatives include the following:



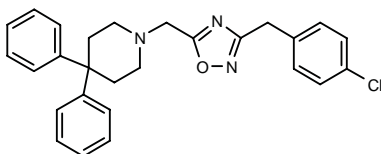
Compound	R1	Formula
300272	CON(Me)2	C ₃₂ H ₃₅ ClN ₄ O ₂
300275	CH2CH2N(Me)2	C ₃₃ H ₃₉ ClN ₄ O



Compound	R1	Formula
300276	NHCH(Et)CH2OH	C ₃₃ H ₃₇ ClN ₄ O ₂
300277	4-Et-1-Piz	C ₃₅ H ₄₀ ClN ₅ O
300278	NHCH(Me)CH2OH	C ₃₂ H ₃₅ ClN ₄ O ₂



300273: C₂₉ H₃₀ Cl N₃



300279: C₂₇ H₂₆ Cl N₃ O

SOURCE – AstraZeneca.

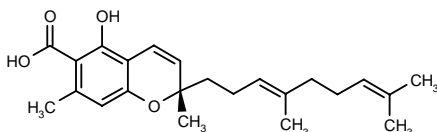
REFERENCES

1. Baxter, A.J.G. et al. (AstraZeneca plc) *Novel diphenyl-piperidine derivative*. WO 0105782.

DAURICHROMENIC ACID

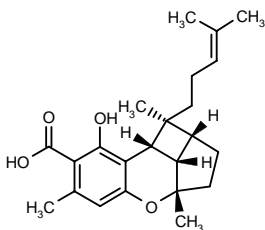
301975

2(*S*)-[4,8-Dimethyl-3(*E*),7-nonadienyl]-5-hydroxy-2,7-dimethyl-2*H*-1-benzopyran-6-carboxylic acid



C₂₃ H₃₀ O₄; Mol wt: 370.4860

ACTION – Chromane derivative isolated from the leaves and twigs of *Rhododendron dauricum* with potent anti-HIV activity in acutely infected H9 cells (IC₅₀ = 5.67 ng/ml) and a therapeutic index of 3,710. A potential new lead for the development of anti-HIV agents. Another related compound is:



Rhododaurichromenic acid A [301976]: C₂₃ H₃₀ O₄

SOURCES – BBI Biotech Research Laboratories; Welfide.

REFERENCES

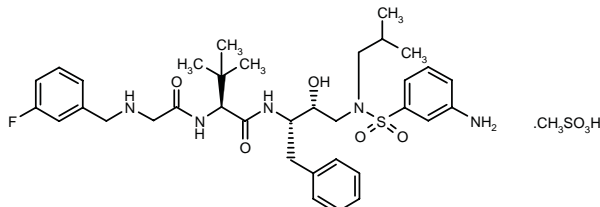
1. Kashiwada, Y. et al. *Isolation of rhododaurichromenic acid B and the anti-HIV principles rhododaurichromenic acid A and rhododaurichromenic acid from Rhododendron dauricum*. Tetrahedron 2001, 57(8): 1559.

DPC-681*

292582

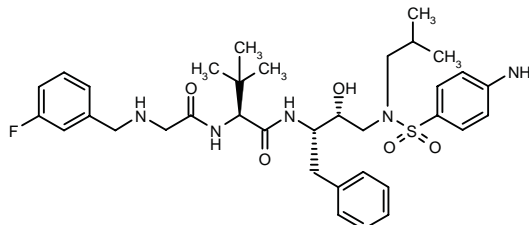
N-(3-Fluorobenzyl)glycyl-L-*tert*-leucine 3-[*N*-(3-amino-phenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-hydroxypropylamide mesylate

N-[3-[*N*-(3-Aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-hydroxypropyl]-2(*S*)-[2-(3-fluorobenzyl-amino)acetamido]-3,3-dimethylbutyramide mesylate



C₃₅ H₄₈ F N₅ O₅ S . CH₄ O₃ S; Mol wt: 765.9638

ACTION – Potent and selective HIV protease inhibitor (K_i = 10-20 pM), a substituted sulfonamide with potent antiviral activity against both wild-type HIV-1 (EC₉₀ = 5 nM) and virus variants that are highly resistant to ritonavir, indinavir, nelfinavir and amprenavir. In dogs, 30 mg/kg p.o. resulted in plasma concentrations exceeding those needed for antiviral efficacy for 4-6 h. Phase I clinical studies are in progress. Another related compound, also in phase I clinical studies, is:



DPC-684 [292583]:** C₃₅ H₄₈ F N₅ O₅ S

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Kaltenbach, R.F. and Trainor, G.L. (DuPont Pharmaceuticals Company). *Bis-amino acid sulfonamides containing N-terminally a subst. benzyl group as HIV protease inhibitors*. WO 0042060.
2. Bachele, L.T. et al. *Resistance profiles of second generation HIV protease inhibitors DPC 681 and DPC 684*. Antivir Ther 2001, 6(Suppl. 1): Abst 6.
3. Erickson Viltanen, S. et al. *DPC 681 and DPC 684: Selective inhibitors of the viral protease active against resistant variants of HIV*. 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst WeOrA532.
4. Erickson-Vitanen, S. et al. *DPC 681 and DPC 684: Resistance and cross-resistance profiles of second generation HIV protease inhibitors*. 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 11.
5. Trainor, G.L. *Search for next generation HIV protease inhibitors: The discovery of DPC 681 and DPC 684*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 188.

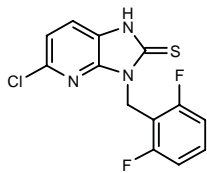
*Identified compound **292582** Drug Data Rep 2000, 022(11). 1018.

Identified compound **292583 (see **292582**) Drug Data Rep 2000, 022(11): 1018.

GP-38

302165

5-Chloro-3-(2,6-difluorobenzyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridine-2-thione



C13 H8 Cl F2 N3 S; Mol wt: 311.7422

ACTION – Anti-HIV-1 agent, an inhibitor of HIV reverse transcriptase shown to inhibit HIV-1 replication in MT-4, CEM and peripheral blood mononuclear cells (PBMCs) with IC₅₀s of about 2 µM and no cytotoxicity up to 80 µM. Compound was effective against various clinical isolates and HIV-1 strains bearing mutations characteristic of nucleoside reverse transcriptase inhibitor resistance, but was inactive against HIV-2 strains.

SOURCES – Universität Innsbruck, Innsbruck (AT); Rega Institute for Medical Research, Leuven (BE).

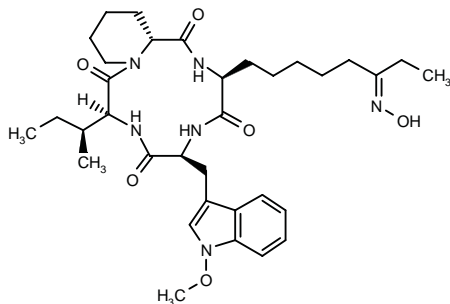
REFERENCES

1. Pannecouque, C. et al. *Synthesis and biological activity of 1-substituted benzimidazole-2-thione analogues: A new class of human immunodeficiency virus reverse transcriptase inhibitors.* Antivir Res 2001, 50(1): Abst 25.

TREATMENT OF PROTOZOAL DISEASES

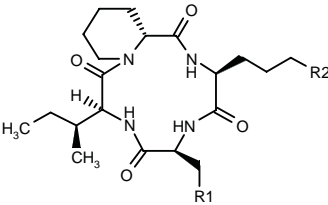
300524

(3*S*,6*S*,9*S*,15*aR*)-3-[(*E*)-6-(Hydroxyimino)octyl]-6-(1-methoxy-1*H*-indol-3-ylmethyl)-9-[1(*S*)-methylpropyl]-perhydropyrido[1,2-*a*][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetrone

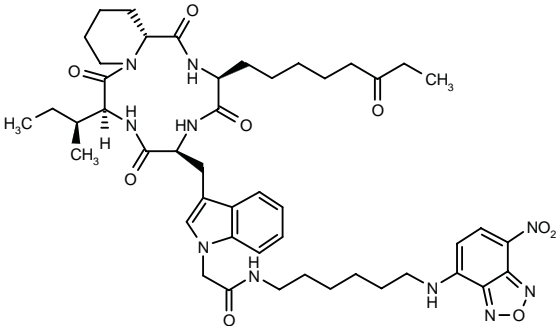


C34 H50 N6 O6; Mol wt: 638.8050

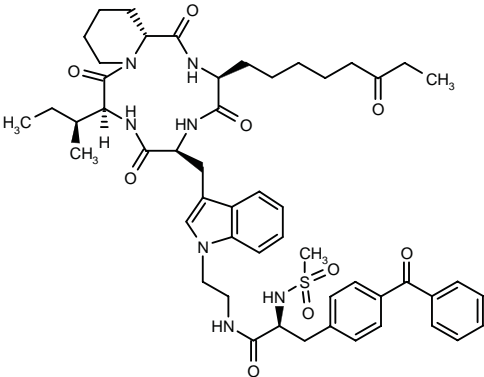
ACTION – Antiprotozoal agent particularly useful in the treatment or prevention of malaria, toxoplasmosis, cryptosporidiosis, trypanosomiasis and coccidiosis, an inhibitor of histone deacetylase. Other compounds from this series of cyclic tetrapeptides derived from apicidin include the following:



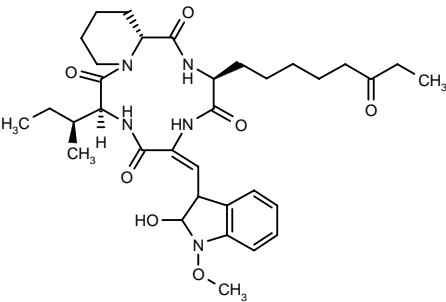
Compound	R1	R2	Formula
300525	1-MeO-3-indolyl	CH2CH2CONHOCH2Ph	C ₃₉ H ₅₂ N ₆ O ₇
300526	1-MeO-3-indolyl	CH2CH(OH)Me	C ₃₂ H ₄₇ N ₅ O ₆
300527	1-MeO-3-indolyl	4-NO2-PhOCOO	C ₃₆ H ₄₄ N ₆ O ₁₀
300534	CH2OPh	CH2CH2CH(OH)Et	C ₃₂ H ₅₀ N ₄ O ₆



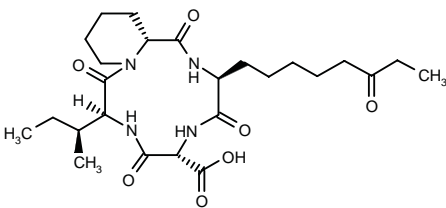
300528: C47 H64 N10 O9



300529: C52 H67 N7 O9 S



300530: C34 H49 N5 O7



300533: C25 H40 N4 O7

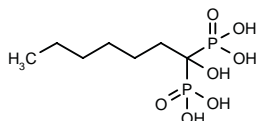
SOURCE – Merck & Co.

REFERENCES

1. Meinke, P.T. et al. (Merck & Co., Inc.) *Apicidin-derived cyclic tetrapeptides*. WO 0107042.

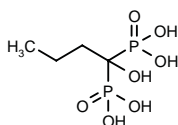
302649

1-Hydroxyheptylidene-1,1-diphosphonic acid



C7 H18 O7 P2; Mol wt: 276.1602

ACTION – Antiprotozoal agent active against *Trypanosoma cruzi*, a bisphosphonate proven to inhibit the growth of intracellular *T. cruzi* amastigotes with an IC_{50} of 18.1 μ M. Compound appear to lack systemic toxicity and represents a lead structure for the development of new candidates for the chemoprophylaxis of trypanosomiasis.



302648: C4 H12 O7 P2

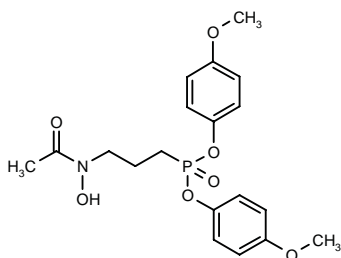
SOURCES – Universidad de Buenos Aires, Buenos Aires (AR); University of Illinois, Urbana-Champaign, IL (US).

REFERENCES

1. Szajmnan, S.H. et al. *Bisphosphonates derived from fatty acids are potent growth inhibitors of Trypanosoma cruzi*. Bioorg Med Chem Lett 2001, 11(6): 789.

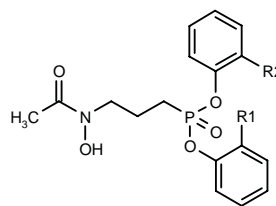
302713

3-(*N*-Acetyl-*N*-hydroxyamino)propylphosphonic acid bis-(4-methoxyphenyl) diester



C19 H24 N O7 P; Mol wt: 409.3726

ACTION – Antimalarial drug, a diaryl ester prodrug of FR-900098⁺ with improved *in vivo* antimalarial activity. In mice infected with the rodent malaria parasite *Plasmodium vinckei*, compound at 0.16 mmol/kg p.o. almost completely reduced parasitemia 6 days after infection, with efficacy superior to that of oral FR-900098 and equivalent to that of i.p. FR-900098. Other related compounds are:



Compound	R1=R2	Formula
302711	H	C ₁₇ H ₂₀ NO ₅ P
302712	Me	C ₁₉ H ₂₄ NO ₅ P

SOURCES – Jomaa Pharmaka; Justus-Liebig-Universität Giessen, Giessen (DE); Philipps-Universität Marburg, Marburg (DE).

REFERENCES

1. Reichenberg, A. et al. *Diaryl ester prodrugs of FR900098 with improved in vivo antimalarial activity*. Bioorg Med Chem Lett 2001, 11(6): 833.

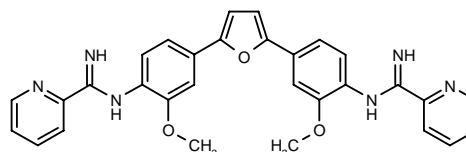
*Drug Data Rep 2000, 022(01): 0076.

DB-745

301689

N,N'-[2,5-Furandiylbis(2-methoxy-4,1-phenylene)]-bis[pyridine-2-carboxamide]

2,5-Bis[3-methoxy-4-[1-(2-pyridyl)-1-iminomethylamino]-phenyl]furan



C30 H26 N6 O3; Mol wt: 518.5744

ACTION – Antiprotozoal agent, a reversed amidine analogue of furamidine active against *Trypanosoma brucei rhodesiense* (IC_{50} = 0.0078 μ g/ml), with a potency about 10-fold lower than that of furamidine and pentamidine. In contrast, compound was at least 10 times more effective than furamidine and pentamidine against *Trypanosoma cruzi*, with activity comparable to that of benznidazole.

SOURCES – Georgia State University, Atlanta, GA (US); University of North Carolina, Chapel Hill, NC (US).

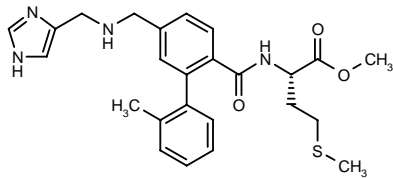
REFERENCES

1. Stephens, C.E. et al. *Synthesis and antitrypanosomal activity of novel dicationic "reversed amidines" in the 2,5-diarylfuran series*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 199.

FTI-2153^{1,3-5,7-9}

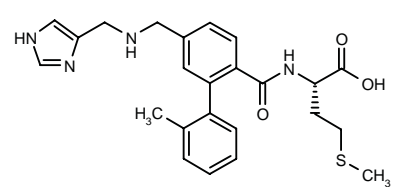
274457

N-[5-(1*H*-Imidazol-4-ylmethylaminomethyl)-2'-methyl-biphenyl-2-ylcarbonyl]-L-methionine methyl ester



C25 H30 N4 O3 S; Mol wt: 466.6030

ACTION – Methyl ester prodrug of the one of the most potent non-thiol-containing farnesyltransferase inhibitors **FTI-2148** (IC₅₀ = 0.001 μM), proven to inhibit the growth of *Plasmodium falciparum* with an ED₅₀ of 2 μg/ml and 99% inhibition at 20 μM. The antiparasitic activity of this inhibitor is currently being evaluated in animal models of malaria. Other experiments indicated that compound strongly and selectively suppressed H-Ras processing (IC₅₀ = 30 nM) and was very effective at blocking oncogenic H-Ras activation of mitogen-activated protein kinase (MAPK) and human tumor growth in soft agar. Compound was found to accumulate in human lung A-549 cells in the mitosis phase of the cell cycle by a mechanism that involves blockade of bipolar spindle formation and chromosome alignment. Potentially useful for the treatment of malaria, as well as in combination therapy regimens with other chemotherapeutic drugs for the treatment of cancer.



FTI-2148 [280577]^{2,6-10}: C24 H28 N4 O3 S

SOURCES – H. Lee Moffitt Center, Tampa, FL (US); London School of Hygiene and Tropical Medicine, London, (GB); Seattle Biomedical Research Institute, Seattle, WA (US); University of Washington, Seattle, WA (US); Yale University, New Haven, CT (US).

REFERENCES

1. Adnane, J. et al. *Upregulation of RhoB transcription, not inhibition of RhoB prenylation, as a potential mechanism by which farnesyltransferase and geranylgeranyltransferase I inhibitors suppress human tumor growth.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1406.

2. Crespo, N. et al. *Constitutively activated Akt-2 blocks the ability of FTI-2148 to inhibit the growth and to induce apoptosis of the human ovarian carcinoma OCVAR3 in nude mice.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1403.

3. Crespo, N. et al. *FTI-2153 inhibits bipolar spindle fomation in human cancer cells: A mechanism for FTI-induced mitotic arrest.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2619.

4. Crespo, N.C. et al. *FTI-2153 inhibits progression through mitosis by accumulating cancer cells in phosphase.* Proc Amer Assoc Cancer Res 2000, 41: Abst 1397.

5. Crespo, N.C. et al. *The farnesyltransferase inhibitor, FTI-2153, blocks bipolar spindle formation and chromosome alignment and causes prometaphase accumulation during mitosis of human lung cancer cells.* J Biol Chem 2001, 276(19): 16161.

6. Ohkanda, J. et al. *Novel nonthiol inhibitors of farnesyl transferase show potent antitumor properties.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 212.

7. Ohkanda, J. et al. *Peptidomimetic inhibitors of protein farnesyltransferase show potent antimalarial activity.* Bioorg Med Chem Lett 2001, 11(6): 761.

8. Sun, J. et al. *Antitumor efficacy of a novel class of non-thiol-containing peptidomimetic inhibitors of farnesyltransferase and geranylgeranyltransferase I: Combination therapy with the cytotoxic agents cisplatin, Taxol, and gemcitabine.* Cancer Res 1999, 59(19): 4919.

9. Sun, J. et al. *Effective combination therapy with the non-thiol farnesyltransferase inhibitor FTI-2148 and taxol, gemcitabine or cisplatin for human tumor xenografts in nude mice.* Proc Amer Assoc Cancer Res 1999, 40: Abst 3443.

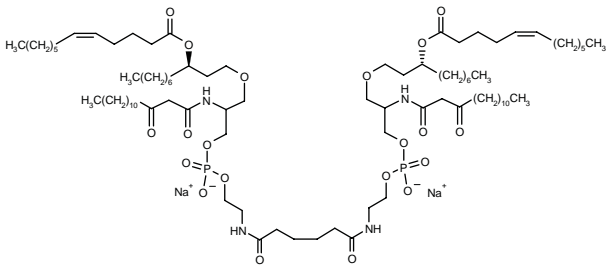
10. Sun, J. et al. *Loss of p21WAF1/CIP1 results in delayed FTI-2148-induced mammary tumor regression and accelerated tumor regrowth after FTI removal in an oncogenic H-ras transgenic mouse model.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2620.

TREATMENT OF SEPTIC SHOCK

ER-112022

300059

(5*Z*,5'*Z*)-5-Dodecenoic acid (1*R*,32*R*)-6,27-bis(3-oxotetra-decanamido)-1,32-diheptyl-9,24-dihydroxy-9,24-dioxido-14,19-dioxo-4,8,10,23,25,29-hexaoxa-13,20-diaza-9,24-diphosphadotriacontane-1,32-diyl ester disodium salt



C88 H162 N4 Na2 O20 P2; Mol wt: 1704.1840

ACTION – Acyclic lipid A analogue proven to activate cells via the lipopolysaccharide (LPS) signaling pathway. Compound induced activation of CHO-L1 fibroblasts and human astrocytoma U373 cells under serum-free conditions, but it was unable to activate cell lines deficient in their ability to respond to LPS such as mutated CHO/CD14 cells. Potentially useful for the treatment of endotoxin-related diseases including Gram-negative bacterial septic shock.

SOURCE – Eisai.

REFERENCES

1. Hawkins, L.D. et al. (Eisai Co., Ltd.) *Immunological adjuvant cpd.* WO 0044758.

2. Lien, E. et al. *A novel acyclic lipid a-like agonist activates cells via the lipolysaccharide signaling pathway.* J Endotoxin Res 2000, 6(2): Abst 023.

3. Lien, E. et al. *A novel acyclic lipopolysaccharide-like agonist activates cells via the lipopolysaccharide signaling pathway.* Scand J Immunol 2000, 51(Suppl. 1): Abst 1.36.

4. Lien, E. et al. *A novel synthetic acyclic lipid A-like agonist activates cells via the lipopolysaccharide/toll-like receptor 4 signaling pathway.* J Biol Chem 2001, 276(3): 1873.

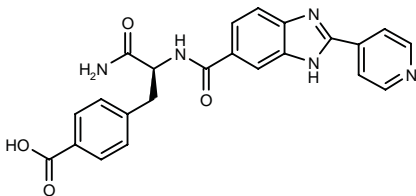
TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

299374

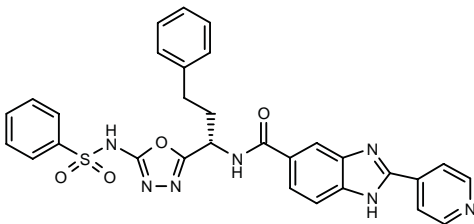
4-Carboxy-*N*²-[2-(4-pyridinyl)-1*H*-benzimidazol-6-yl-carbonyl]-*L*-phenylalaninamide

4-[2(*S*)-Carbamoyl-2-[2-(4-(4-pyridyl)-1*H*-benzimidazol-6-ylcarbonyl)ethyl]benzoic acid



C23 H19 N5 O4; Mol wt: 429.4341

ACTION – Agent for the treatment or prevention of diseases involving increased activity of NF-κB such as rheumatoid arthritis, osteoarthritis, asthma, myocardial infarction, Alzheimer’s disease, cancer and atherosclerosis that acts by selectively inhibiting IκBkinase, as demonstrated *in vitro* by an IC₅₀ value of 7 μM for inhibition of IκB kinase, while it gave 0% inhibition of protein kinase A, protein kinase C and casein kinase II at 100 μM. Another exemplified compounds from this series of substituted benzimidazole derivatives is:



299375: C30 H25 N7 O4 S

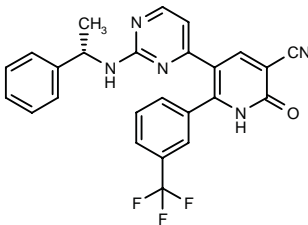
SOURCE – Aventis Pharma.

REFERENCES

1. Ritzeler, O. et al. (Aventis Pharma Deutschland GmbH) *Subst. benzimidazole*. WO 0100610.

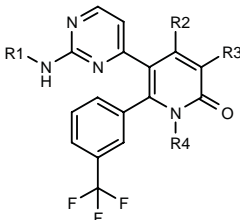
299471

2-Oxo-5-[2-[1(*S*)-phenylethylamino]pyrimidin-4-yl]-6-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carbonitrile

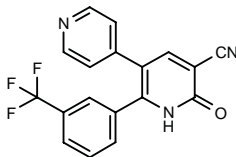


C25 H18 F3 N5 O; Mol wt: 461.4452

ACTION – An inhibitor of the production or activity of cytokines such as IL-1, IL-6, IL-8 and TNF-α with potential utility in the treatment of a broad range of cytokine-mediated conditions including rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, septic shock, tuberculosis, atherosclerosis, muscle degeneration, cachexia, gout, adult respiratory distress syndrome, bone resorption diseases, transplant rejection and fever. Other specifically claimed compounds from this series of substituted pyridones are:



Compound	R1	R2	R3	R4	Isomer	Formula
299473	(CH2)3OEt	H	CN	H		C ₂₂ H ₂₀ F ₃ N ₅ O ₂
299474	Ph	H	CN	H		C ₂₃ H ₁₄ F ₃ N ₅ O
299475	(S)-CH(Me)Ph	H	H	H		C ₂₄ H ₁₉ F ₃ N ₄ O
299477	(S)-CH(Me)Ph	Me	CN	H		C ₂₆ H ₂₀ F ₃ N ₅ O
299478	(S)-CH(Me)Ph	H	CH2NH2	H		C ₂₅ H ₂₂ F ₃ N ₅ O
299479	(S)-CH(Me)Ph	H	CO2Et	H		C ₂₇ H ₂₃ F ₃ N ₄ O ₃
299480	(S)-CH(Me)Ph	H	NO2	H		C ₂₄ H ₁₈ F ₃ N ₅ O ₃
299481	(S)-CH(Me)Ph	H	CN	Me		C ₂₆ H ₂₀ F ₃ N ₅ O
299482	(S)-CH(Me)Ph	H	CO2H	H		C ₂₅ H ₁₉ F ₃ N ₄ O ₃
299483	(S)-CH(Me)Ph	H	1-Pip-CO	H		C ₃₀ H ₂₈ F ₃ N ₅ O ₂
299484	(S)-CH(Me)Ph	H	3-quinuclidinyl-NHCO	H	racemic	C ₃₃ H ₃₁ F ₃ N ₆ O ₂
299485	(S)-CH(Me)Ph	H	CONH2	H		C ₂₅ H ₂₀ F ₃ N ₅ O ₂
299486	(S)-CH(Me)Ph	H	3-NH2-1-Pip-CO	H		C ₃₀ H ₂₉ F ₃ N ₆ O ₂
299487	(S)-CH(Me)Ph	H	4-Pip-NHCO	H		C ₃₀ H ₂₉ F ₃ N ₆ O ₂



299476: C18 H10 F3 N3 O

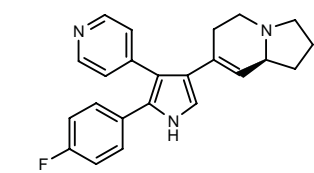
SOURCE – Merck & Co.

REFERENCES

1. Liverton, N.J. et al. (Merck & Co., Inc.) *Subst. pyridones having cytokine inhibitory activity*. WO 0100208.

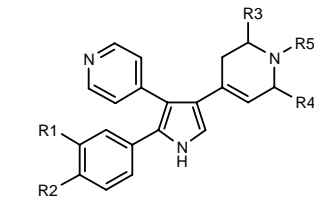
299626

(-)-(8a*S*)-7-[5-(4-Fluorophenyl)-4-(4-pyridinyl)-1*H*-pyrrol-3-yl]-1,2,3,5,6,8a-hexahydroindolizine



C23 H22 F N3; Mol wt: 359.4458

ACTION – An inhibitor of the production of inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF- α , particularly IL-1 and TNF- α , with potential for the treatment or prevention of cytokine-mediated disorders such as inflammatory diseases, bone resorption, viral infections, pain, rheumatoid arthritis, osteoarthritis, cancer and hepatitis. *In vitro*, compound inhibited the lipopolysaccharide-stimulated production of TNF- α in human peripheral blood with an IC₅₀ value of 0.026 μ M. Other exemplified compounds from this series of heteroaryl-substituted pyrrole derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
299627	H	F	-(CH2)2-		H	C ₂₂ H ₂₀ FN ₃
299628	H	F	H	H	CH2CH2Ph	C ₂₈ H ₂₆ FN ₃
299629	H	F	H		-(CH2)3-	C ₂₃ H ₂₂ FN ₃
299630	H	F	H	Me	Pr	C ₂₄ H ₂₆ FN ₃
299631	H	F	Me	H	Pr	C ₂₄ H ₂₆ FN ₃
299632	H	F	H		-(CH2)4-	C ₂₄ H ₂₄ FN ₃
299633	F	F	H		-(CH2)3-	C ₂₃ H ₂₁ F ₂ N ₃
299634	CF3	H	H		-(CH2)3-	C ₂₄ H ₂₂ F ₃ N ₃

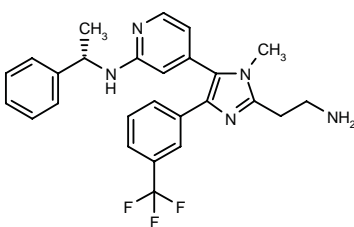
SOURCE – Sankyo.

REFERENCES

1. Aoki, K. et al. (Sankyo Co., Ltd.) *Heteroaryl-substd. pyrrole derivs., their preparation and their therapeutic uses*. EP 1070711.

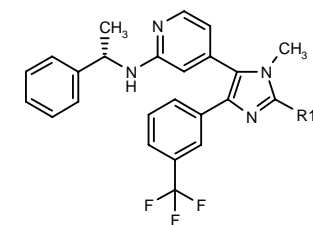
299681

4-[2-(2-Aminoethyl)-1-methyl-4-[3-(trifluoromethyl)phenyl]-1*H*-imidazol-5-yl]-*N*-[1(*S*)-phenylethyl]pyridin-2-amine



C26 H26 F3 N5; Mol wt: 465.5204

ACTION – An inhibitor of the production or activity of cytokines such as IL-1, IL-6, IL-8 and TNF- α with potential for the treatment of a broad range of cytokine-mediated conditions including rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, septic shock, tuberculosis, atherosclerosis, muscle degeneration, cachexia, gout, adult respiratory distress syndrome, bone resorption diseases, transplant rejection and fever. Other specifically claimed compounds from this series of substituted imidazole derivatives are:



Compound	R1	Formula
299682	(<i>R</i>)-CH(Me)NH2	C ₂₆ H ₂₆ F ₃ N ₅
299683	3-azetidiny-CH2	C ₂₈ H ₂₈ F ₃ N ₅
299684	CH2NH2	C ₂₅ H ₂₄ F ₃ N ₅
299685	CH2N(Me)2	C ₂₇ H ₂₈ F ₃ N ₅
299686	(CH2)3N(Me)2	C ₂₉ H ₃₂ F ₃ N ₅
299687	(CH2)3NH2	C ₂₇ H ₂₈ F ₃ N ₅
299688	4-morpholinyl-CH2	C ₂₉ H ₃₀ F ₃ N ₅ O
299689	(CH2)3NHMe	C ₂₈ H ₃₀ F ₃ N ₅
299690	CH2CH2N(Me)2	C ₂₈ H ₃₀ F ₃ N ₅

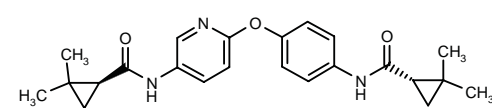
SOURCE – Merck & Co.

REFERENCES

1. Claiborne, C.F. et al. (Merck & Co., Inc.) *Cpds. having cytokine inhibitory activity*. WO 0101988.

299820

N-[6-[4-[(1*S*)-2,2-Dimethylcyclopropylcarboxamido]-phenoxy]pyridin-3-yl]-2,2-dimethylcyclopropane-1(*S*)-carboxamide



C23 H27 N3 O3; Mol wt: 393.4843

ACTION – An inhibitor of AP-1 and NF- κ B activation, also reported to inhibit inflammatory cytokine production, matrix metalloproteinases and cell adhesion factor expression, with potential as an antiinflammatory, anti-rheumatic, immunosuppressive and antimetastatic agent, as well as for the treatment of arteriosclerosis and viral infections. *In vitro*, compound inhibited IL-1 β -stimulated NF- κ B activity in human umbilical vein endothelial cells (HUVEC) with an IC₅₀ of 0.25 μ g/ml. In addition, compound is reported to inhibit a delayed hypersensitivity reaction in rhesus monkeys at 50 mg/kg/day p.o. b.i.d. x 4 weeks.

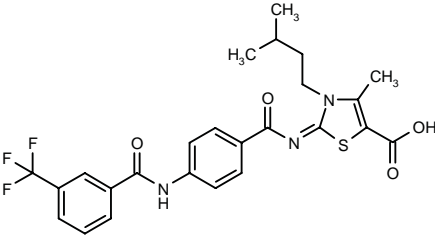
SOURCE – Ajinomoto.

REFERENCES

1. Iino, Y. et al. (Ajinomoto Co., Inc.) *Heterocyclic cpds. and medicinal use thereof*. WO 0102359.

300058

4-Methyl-3-(3-methylbutyl)-2-[4-[3-(trifluoromethyl)-benzamido]benzoylimino]-2,3-dihydrothiazole-5-carboxylic acid



C25 H24 F3 N3 O4 S; Mol wt: 519.5416

ACTION – A VCAM-1/VLA-4 inhibitor with an IC₅₀ value of 2.3 μM in a VCAM-1/VLA-4 Ramos cell-based assay, potentially useful for the treatment of acute and chronic inflammatory disorders, as well as arteriosclerosis. A representative compound from a series of thiazoline derivatives.

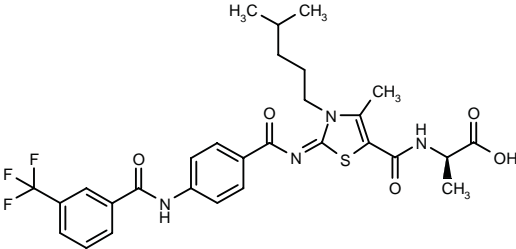
SOURCE – Taisho.

REFERENCES

1. Sato, M. and Ishii, T. (Taisho Pharmaceutical Co., Ltd.) *Thiazoline derivs.* JP 2001002665.

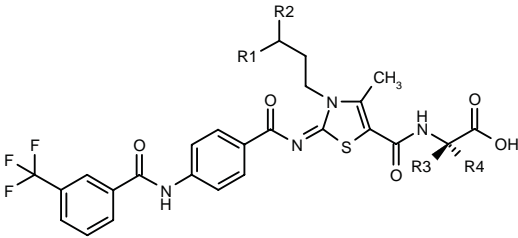
300060

N-[4-Methyl-3-(4-methylpentyl)-2-[4-[3-(trifluoromethyl)-benzamido]benzoylimino]-2,3-dihydrothiazol-5-ylcarbonyl]-D-alanine



C29 H31 F3 N4 O5 S; Mol wt: 604.6469

ACTION – A VCAM-1/VLA-4 inhibitor with an IC₅₀ value of 1.9 μM in a VCAM-1/VLA-4 Ramos cell-based assay, potentially useful for the treatment of acute and chronic inflammatory disorders, as well as arteriosclerosis. Other exemplified compounds from this series of thiazoline alanine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
300062	Me	Me	H	Me	C ₂₈ H ₂₉ F ₃ N ₄ O ₅ S
300063	Pr	H	H	Me	C ₂₉ H ₃₁ F ₃ N ₄ O ₅ S
300065	Me	Me	Me	H	C ₂₈ H ₂₉ F ₃ N ₄ O ₅ S
300066	Pr	H	Me	H	C ₂₉ H ₃₁ F ₃ N ₄ O ₅ S
300067	i-Pr	H	H	Me	C ₂₉ H ₃₁ F ₃ N ₄ O ₅ S

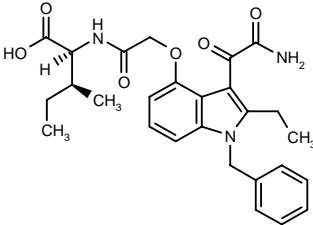
SOURCE – Taisho.

REFERENCES

1. Sato, M. and Ishii, T. (Taisho Pharmaceutical Co., Ltd.) *Alanine derivs.* JP 2001002664.

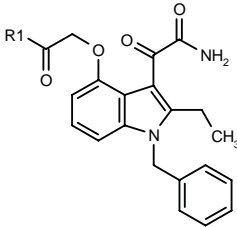
300315

N-[2-[3-(2-Amino-2-oxoacetyl)-1-benzyl-2-ethyl-1 H-indol-4-yloxy]acetyl]-L-isoleucine



C27 H31 N3 O6; Mol wt: 493.5569

ACTION – Human nonpancreatic secretory phospholipase A₂ (sPLA₂; IC₅₀ = 25.1 nM) inhibitor, with potential for the treatment of inflammatory disorders such as sepsis and rheumatoid arthritis. Within this series of indole derivatives, the following compounds are also included:



Compound	R1	Formula
300316	OMe	C ₂₂ H ₂₂ N ₂ O ₅
300317	-L-Leu-OMe	C ₂₈ H ₃₃ N ₃ O ₆
300318	NHCH ₂ CO ₂ H	C ₂₃ H ₂₃ N ₃ O ₆
300320	-L-Ala-OH	C ₂₄ H ₂₅ N ₃ O ₆
300321	-L-Leu-OH	C ₂₇ H ₃₁ N ₃ O ₆
300322	-L-Phe-OH	C ₃₀ H ₂₉ N ₃ O ₆
300323	NHCH(CO ₂ H) ₂	C ₂₄ H ₂₃ N ₃ O ₈
300325	-L-Val-OH	C ₂₆ H ₂₉ N ₃ O ₆

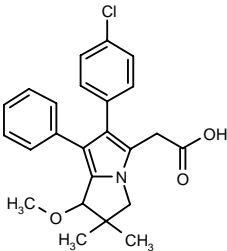
SOURCE – Lilly.

REFERENCES

1. Lin, H.-S. and Richett, M.E. (Eli Lilly and Company) *sPLA₂ inhibitors*. WO 0105761.

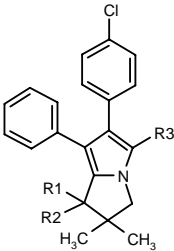
300342

2-[6-(4-Chlorophenyl)-1-methoxy-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl]acetic acid



C24 H24 Cl N O3; Mol wt: 409.9106

ACTION – Antiinflammatory agent that acts by inhibiting cyclooxygenase type 1 (COX-1; IC₅₀ = 0.06 μmol) and 5-lipoxygenase (5-LO; IC₅₀ = 0.04 μmol). Other exemplified compounds from this series of oxo and hydroxy derivatives of pyrrolizines include the following:



Compound	R1	R2	R3	Formula
300343	-O-		H	C ₂₁ H ₁₈ ClNO
300344	OMe	H	Me	C ₂₃ H ₂₄ ClNO
300345	-O-		CH ₂ CO ₂ H	C ₂₃ H ₂₀ ClNO ₃

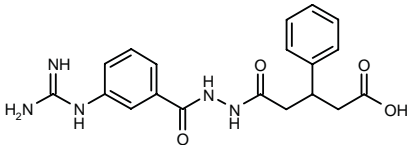
SOURCE – Merckle.

REFERENCES

1. Laufer, S. et al. (Merckle GmbH) *Anti-inflammatory oxo derivs. and hydroxy derivs. of pyrrolizines, and their pharmaceutical use*. WO 0105792.

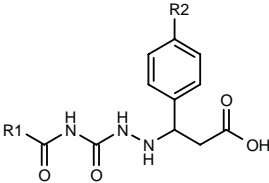
300400

5-[2-(3-Guanidinobenzoyl)hydrazino]-5-oxo-3-phenyl-pentanoic acid

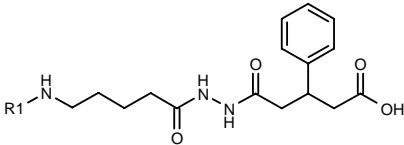


C19 H21 N5 O4; Mol wt: 383.4059

ACTION – An integrin inhibitor that is potentially useful for the treatment of thrombosis, myocardial infarction, cardiovascular diseases, arteriosclerosis, inflammation, tumors, osteoporosis and infections, particularly for angiogenesis-associated diseases such as tumors and rheumatoid arthritis. Other specifically claimed diacylhydrazine derivatives are:



Compound	R1	R2	Formula
300401	3-[NH ₂ C(=NH)NH]-PhCH ₂	H	C ₁₉ H ₂₂ N ₆ O ₄
300402	3-[NH ₂ C(=NH)NH]-Ph	H	C ₁₈ H ₂₀ N ₆ O ₄
300404	(CH ₂) ₄ NHC(=NH)NH ₂	H	C ₁₆ H ₂₄ N ₆ O ₄
300406	3-[NH ₂ C(=NH)NH]-Ph	Cl	C ₁₈ H ₁₉ ClN ₆ O ₄
300407	4-Me-2-Pyr-NH(CH ₂) ₄	Cl	C ₂₁ H ₂₆ ClN ₅ O ₄
300408	(CH ₂) ₄ NHC(=NH)NH ₂	Cl	C ₁₆ H ₂₃ ClN ₆ O ₄



Compound	R1	Formula
300403	4-Me-2-Pyr	C ₂₂ H ₂₈ N ₄ O ₄
300405	C(=NH)NH ₂	C ₁₇ H ₂₅ N ₅ O ₄

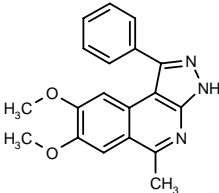
SOURCE – Merck KGaA.

REFERENCES

1. Holzemann, G. et al. (Merck Patent GmbH) *Diacylhydrazine derivs.* DE 19932796, WO 0105753.

300733

7,8-Dimethoxy-5-methyl-1-phenyl-3*H*-pyrazolo[3,4-*c*]-isoquinoline



C19 H17 N3 O2; Mol wt: 319.3623

ACTION – Antiinflammatory and antiproliferative agent, an inhibitor of lipopolysaccharide (LPS)-induced TNF- α production in RAW264.7 cells and murine peritoneal macrophages similar to SB-203580, a specific inhibitor of p38 MAP kinase (IC_{50} = 10 and 1 μ M, respectively). Unlike SB-203580, however, compound did not strongly inhibit p38 MAP kinase activity and the suppression of LPS-induced TNF- α production could be attributed to another mechanism of action. *In vivo*, in a mouse model of endotoxic shock, compound inhibited the LPS-induced increase in serum levels of TNF- α with an ED_{50} value of about 10 mg/kg i.p., similar to SB-203580. Compound also inhibited the growth of RAW264.7 and THP-1 cells in a concentration-dependent manner, unlike SB-203580, and its effect appeared to be cytostatic rather than cytotoxic.

SOURCE – Suntory.

REFERENCES

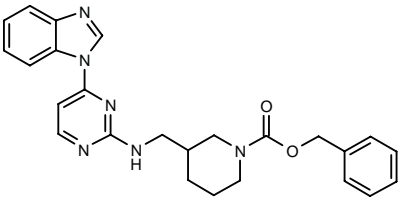
1. Nagahira, A. et al. *Identification of a novel inhibitor of LPS-induced TNF- α production with antiproliferative activity in monocyte/macrophages.* Biochem Biophys Res Commun 2001, 281(4): 1030.

2. Nikolyukin, Y.A. et al. *Synthesis of azolo(5,4-c) isoquinolines.* Chem Heterocycl Compd 1990, 26914.

IMMUNOMODULATING AGENTS

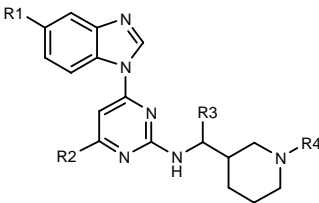
299546

3-[4-(1*H*-Benzimidazol-1-yl)pyrimidin-2-ylaminomethyl]-piperidine-1-carboxylic acid benzyl ester



C25 H26 N6 O2; Mol wt: 442.5204

ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, Fyn(B), Fyn(T), Lyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment and prevention of protein tyrosine kinase-associated disorders such as transplant rejection, rheumatoid arthritis, psoriasis and inflammatory bowel disease. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
299553	H	H	H	1-Naph-NHCO	C ₂₈ H ₂₇ N ₇ O
299554	H	H	Me	CH ₂ CH ₂ -PO(OEt) ₂	C ₂₄ H ₃₅ N ₆ O ₃ P
299555	H	H	Me	2-Cl-PhNHCO	C ₂₅ H ₂₆ ClN ₇ O
299556	t-BuCONH	H	Me	SO ₂ Me	C ₂₄ H ₃₃ N ₇ O ₃ S
299557	NH ₂	H	Me	CONHPh	C ₂₅ H ₂₈ N ₈ O
299558	2-NH ₂ -4-Pyr	H	Me	1-Naph-NHCO	C ₃₄ H ₃₃ N ₉ O
299559	2-NH ₂ -4-pyrimidinyl	2-(CH ₂ OH)-Ph	Me	CONHPh	C ₃₆ H ₃₆ N ₁₀ O ₂

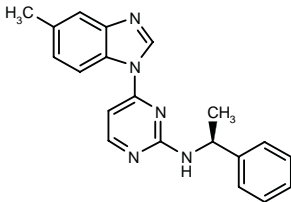
SOURCE – Merck & Co.

REFERENCES

1. Goulet, J.L. et al. (Merck & Co., Inc.) *Src kinase inhibitor cpds.* WO 0100207.

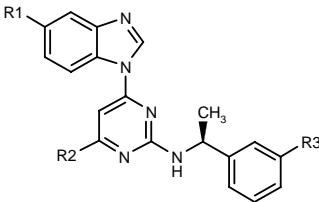
299560

4-(5-Methyl-1*H*-benzimidazol-1-yl)-*N*-[1(*S*)-phenylethyl]-pyrimidin-2-amine



C20 H19 N5; Mol wt: 329.4051

ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, Fyn(B), Fyn(T), Lyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment and prevention of protein tyrosine kinase-associated disorders such as immunological disorders. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	R3	Formula
299562	NHCH ₂ CH ₂ NH ₂	H	H	C ₂₁ H ₂₃ N ₇
299563	i-Pr-NHCONH	H	H	C ₂₃ H ₂₅ N ₇ O
299564	2-furyl	H	H	C ₂₃ H ₁₉ N ₅ O
299565	2-NH ₂ -4-pyrimidinyl	H	H	C ₂₃ H ₂₀ N ₈
299567	2-NH ₂ -4-Pyr	H	H	C ₂₄ H ₂₁ N ₇
299568	4-Pyr	2-Me-Ph	H	C ₃₁ H ₂₆ N ₆
299570	4-Pyr	2-Me-Ph	CF ₃	C ₃₂ H ₂₅ F ₃ N ₆

ACTION – Antiinflammatory and antiproliferative agent, an inhibitor of lipopolysaccharide (LPS)-induced TNF- α production in RAW264.7 cells and murine peritoneal macrophages similar to SB-203580, a specific inhibitor of p38 MAP kinase (IC_{50} = 10 and 1 μ M, respectively). Unlike SB-203580, however, compound did not strongly inhibit p38 MAP kinase activity and the suppression of LPS-induced TNF- α production could be attributed to another mechanism of action. *In vivo*, in a mouse model of endotoxic shock, compound inhibited the LPS-induced increase in serum levels of TNF- α with an ED_{50} value of about 10 mg/kg i.p., similar to SB-203580. Compound also inhibited the growth of RAW264.7 and THP-1 cells in a concentration-dependent manner, unlike SB-203580, and its effect appeared to be cytostatic rather than cytotoxic.

SOURCE – Suntory.

REFERENCES

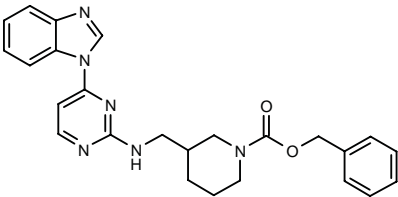
1. Nagahira, A. et al. *Identification of a novel inhibitor of LPS-induced TNF- α production with antiproliferative activity in monocyte/macrophages.* Biochem Biophys Res Commun 2001, 281(4): 1030.

2. Nikolyukin, Y.A. et al. *Synthesis of azolo(5,4-c) isoquinolines.* Chem Heterocycl Compd 1990, 26914.

IMMUNOMODULATING AGENTS

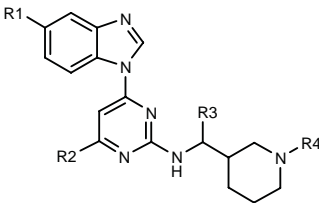
299546

3-[4-(1*H*-Benzimidazol-1-yl)pyrimidin-2-ylaminomethyl]-piperidine-1-carboxylic acid benzyl ester



C25 H26 N6 O2; Mol wt: 442.5204

ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, Fyn(B), Fyn(T), Lyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment and prevention of protein tyrosine kinase-associated disorders such as transplant rejection, rheumatoid arthritis, psoriasis and inflammatory bowel disease. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
299553	H	H	H	1-Naph-NHCO	C ₂₈ H ₂₇ N ₇ O
299554	H	H	Me	CH ₂ CH ₂ -PO(OEt) ₂	C ₂₄ H ₃₅ N ₆ O ₃ P
299555	H	H	Me	2-Cl-PhNHCO	C ₂₅ H ₂₆ ClN ₇ O
299556	t-BuCONH	H	Me	SO ₂ Me	C ₂₄ H ₃₃ N ₇ O ₃ S
299557	NH ₂	H	Me	CONHPh	C ₂₅ H ₂₈ N ₈ O
299558	2-NH ₂ -4-Pyr	H	Me	1-Naph-NHCO	C ₃₄ H ₃₃ N ₉ O
299559	2-NH ₂ -4-pyrimidinyl	2-(CH ₂ OH)-Ph	Me	CONHPh	C ₃₆ H ₃₆ N ₁₀ O ₂

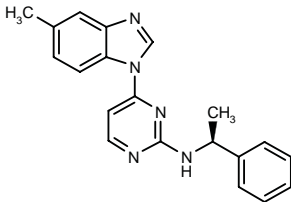
SOURCE – Merck & Co.

REFERENCES

1. Goulet, J.L. et al. (Merck & Co., Inc.) *Src kinase inhibitor cpds.* WO 0100207.

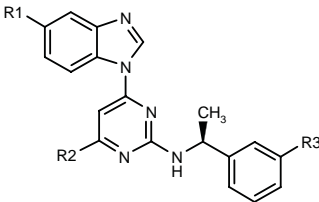
299560

4-(5-Methyl-1*H*-benzimidazol-1-yl)-*N*-[1(*S*)-phenylethyl]-pyrimidin-2-amine

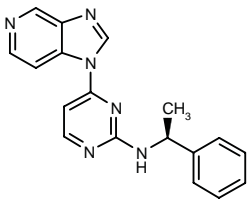


C20 H19 N5; Mol wt: 329.4051

ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, Fyn(B), Fyn(T), Lyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment and prevention of protein tyrosine kinase-associated disorders such as immunological disorders. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	R3	Formula
299562	NHCH ₂ CH ₂ NH ₂	H	H	C ₂₁ H ₂₃ N ₇
299563	i-Pr-NHCONH	H	H	C ₂₃ H ₂₅ N ₇ O
299564	2-furyl	H	H	C ₂₃ H ₁₉ N ₅ O
299565	2-NH ₂ -4-pyrimidinyl	H	H	C ₂₃ H ₂₀ N ₈
299567	2-NH ₂ -4-Pyr	H	H	C ₂₄ H ₂₁ N ₇
299568	4-Pyr	2-Me-Ph	H	C ₃₁ H ₂₆ N ₆
299570	4-Pyr	2-Me-Ph	CF ₃	C ₃₂ H ₂₅ F ₃ N ₆



299561: C18 H16 N6

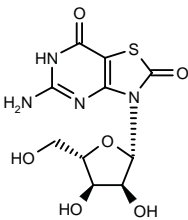
SOURCE – Merck & Co.

REFERENCES

1. Armstrong, H.M. et al. (Merck & Co., Inc.) *Src kinase inhibitor cpds.* WO 0100213.

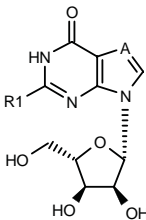
299742

5-Amino-3-(β-L-ribofuranosyl)thiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione



C10 H12 N4 O6 S; Mol wt: 316.2928

ACTION – Immunomodulating agent with the ability to modulate Th1 and Th2 activity, with potential for the treatment of viral, parasitic, protozoal and helminthic infections, cancer and autoimmune diseases. Compound is reported to have increased stability over D-nucleosides, which may lead to an improved pharmacokinetic profile. Other specifically claimed purine L-nucleosides are:



Compound	R1	A	Formula
299743	NH2	-N=	C ₁₀ H ₁₃ N ₅ O ₅
299744	NHAc	-N=	C ₁₂ H ₁₅ N ₅ O ₆
299746	H	-C[C(=NOH)NH2]=	C ₁₂ H ₁₅ N ₅ O ₆

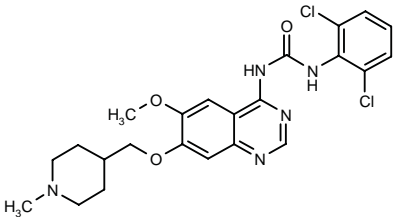
SOURCE – ICN.

REFERENCES

1. Wang, G. et al. (ICN Pharmaceuticals, Inc.) *Purine L-nucleosides, analogs and uses thereof.* EP 1072607.

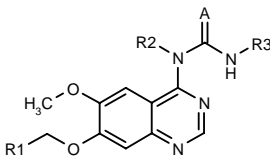
299960

1-(2,6-Dichlorophenyl)-3-[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea

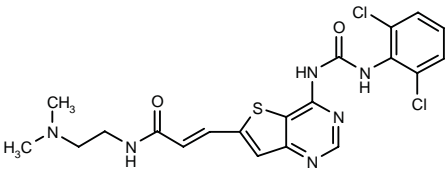


C23 H25 Cl2 N5 O3; Mol wt: 490.3885

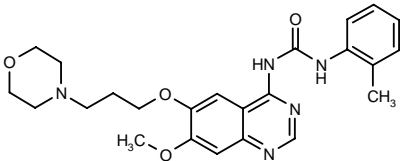
ACTION – Quinazoline derivative that modulates T-cell activation by inhibiting non-receptor tyrosine kinases such as p56^{lck} tyrosine kinase. This compound is expected to be useful for the treatment of T-cell-mediated diseases such as transplant rejection and rheumatoid arthritis. Other exemplified quinazoline derivatives are:



Compound	R1	R2	R3	A	Formula
299961	1-Me-4-Pip	H	2-Cl-Ph	O	C ₂₃ H ₂₆ ClN ₅ O ₃
299962	1-Me-4-Pip	Me	2,6-(Cl)2-Ph	O	C ₂₄ H ₂₇ Cl ₂ N ₅ O ₃
299964	1-Me-4-Pip	H	(S)-CH(Me)Ph	O	C ₂₅ H ₃₁ N ₅ O ₃
299965	4-(t-BuOCONHCH2)-1-Pip-CH2CH2	H	2,6-(Cl)2-Ph	O	C ₃₀ H ₃₈ Cl ₂ N ₆ O ₅
299967	1-Me-4-Pip	H	2,6-(Cl)2-Ph	NH	C ₂₃ H ₂₆ Cl ₂ N ₆ O ₂
299968	1-Me-4-Pip	H	2-Cl-6-Me-Ph	N(Et)	C ₂₆ H ₃₃ ClN ₆ O ₂



299963: C20 H20 Cl2 N6 O2 S



299966: C24 H29 N5 O4

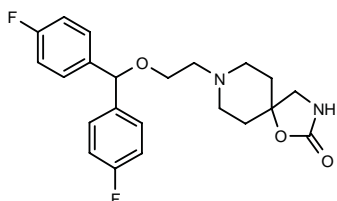
SOURCE – AstraZeneca.

REFERENCES

1. Crawley, G.C. et al. (AstraZeneca plc;AstraZeneca SA) *Quinazoline derivs.* WO 0104102.

300145

8-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one



C22 H24 F2 N2 O3; Mol wt: 402.4386

ACTION – Th1-selective immunosuppressive agent proven to induce IL-4 production in murine T-cells (D10.G4.1) at a concentration of 2.5 µg/ml. *In vivo*, compound was found to delay the development of experimental autoimmune encephalomyelitis in rats at 30 mg/kg/day p.o. x 11 days.

SOURCE – Sankyo.

REFERENCES

1. Shiraishi, A. et al. (Sankyo Co., Ltd.) *Nitrogen-containing saturated heterocyclic cpds.* JP 2001011050.

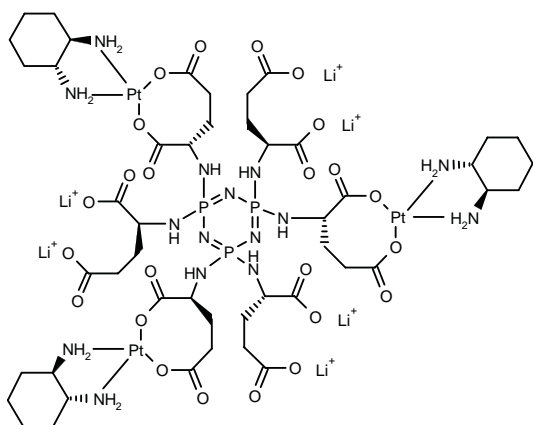
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

KI-60606¹⁻³

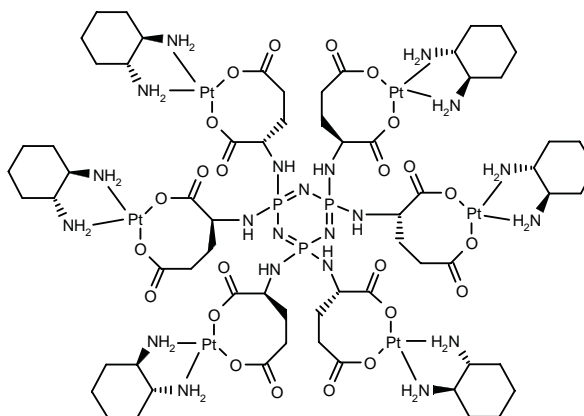
301951

Hexalithium tris(*trans*-cyclohexane-1,2-diamine-κ*N*, κ*N'*)[μ₃-[2,4,6-tris[(1*S*)-1,3-di(carboxy-κ*O*)propylamino]-2,4,6-tris[(1*S*)-1,3-dicarboxypropylamino]-1,3,5,2,4,6-triazatriphosphorinato(12-)]][triplatinate(6-)]



C48 H78 Li6 N15 O24 P3 Pt3; Mol wt: 1969.0330

ACTION – Third-generation platinum antitumor agent with broad-spectrum cytotoxicity against human tumor cells including cisplatin- and doxorubicin-resistant ovarian carcinoma A2780 and colon carcinoma HCT-15 cells (IC₅₀ = 0.27 and 1.89 µM, respectively). Compound also showed excellent *in vivo* activity against sensitive and cisplatin-resistant leukemia L1210, as well as human non-small cell lung cancer A549 xenografts. Pharmacokinetic studies in rats showed that the high antitumor activity of the drug is due to controlled release of the active (dach)Pt(II) moiety. Another related platinum complex is:



301873¹: C66 H120 N21 O24 P3 Pt6

SOURCES – Il-Yang; Korea Institute of Science and Technology, Seoul (KR); Korea Research Institute of Chemical Technology, Taejeon (KR).

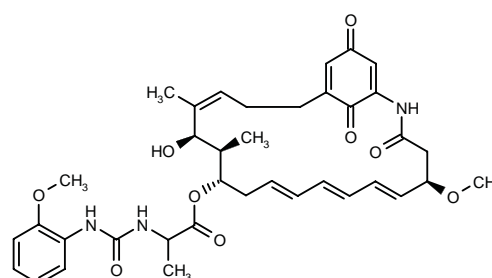
REFERENCES

1. Sohn, Y.S. et al. (Korea Institute of Science and Technology; Il-Yang Pharmaceutical Co., Ltd.) *Platinum complex conjugated to cyclotriphosphazene, its preparation, and anticancer agent comprising the same.* EP 1082331, US 6221906, WO 0058321.
2. Baek, H. et al. *Synthesis and antitumor activity of cyclotriphosphazene-(diamine)platinum (II) conjugates.* Anti-Cancer Drugs 2000, 11(9): 715.
3. Sohn, Y.S. et al. *Antitumor activity pharmacokinetics of a novel platinum(II)-cyclotriphosphazone conjugate drug KI60606.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2047.

ANTIBIOTICS AND ALKALOIDS

299377

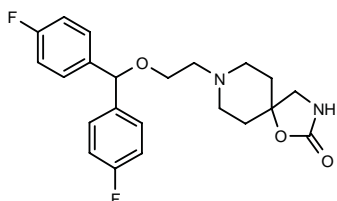
2-(2-Methoxyphenylureido)propanoic acid (5*R*,6*E*,8*E*,10*E*,13*S*,14*R*,15*R*,16*Z*)-15-hydroxy-5-methoxy-14,16-dimethyl-3,22,24-trioxo-2-azabicyclo[18.3.1]tetracos-1(23),6,8,10,16,20-hexaen-13-yl ester



C37 H45 N3 O9; Mol wt: 675.7745

300145

8-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one



C22 H24 F2 N2 O3; Mol wt: 402.4386

ACTION – Th1-selective immunosuppressive agent proven to induce IL-4 production in murine T-cells (D10.G4.1) at a concentration of 2.5 µg/ml. *In vivo*, compound was found to delay the development of experimental autoimmune encephalomyelitis in rats at 30 mg/kg/day p.o. x 11 days.

SOURCE – Sankyo.

REFERENCES

1. Shiraishi, A. et al. (Sankyo Co., Ltd.) *Nitrogen-containing saturated heterocyclic cpds.* JP 2001011050.

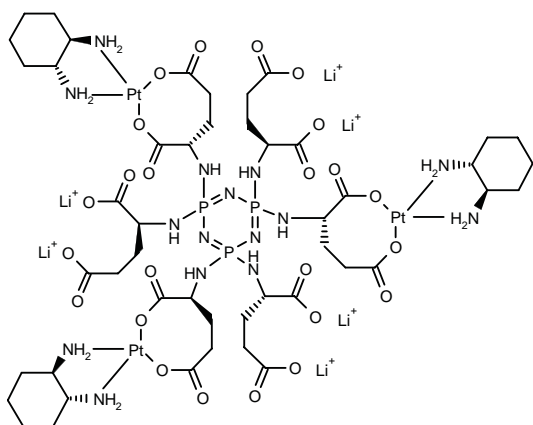
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

KI-60606¹⁻³

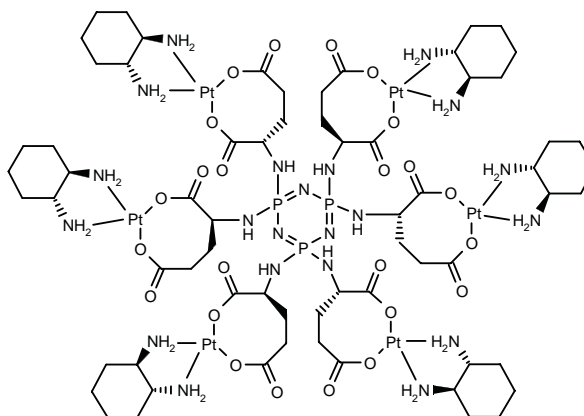
301951

Hexalithium tris(*trans*-cyclohexane-1,2-diamine-κN, κN')[μ₃-[2,4,6-tris[(1*S*)-1,3-di(carboxy-κO)propylamino]-2,4,6-tris[(1*S*)-1,3-dicarboxypropylamino]-1,3,5,2,4,6-triazatriphosphorinato(12-)]][triplatinate(6-)]



C48 H78 Li6 N15 O24 P3 Pt3; Mol wt: 1969.0330

ACTION – Third-generation platinum antitumor agent with broad-spectrum cytotoxicity against human tumor cells including cisplatin- and doxorubicin-resistant ovarian carcinoma A2780 and colon carcinoma HCT-15 cells (IC₅₀ = 0.27 and 1.89 µM, respectively). Compound also showed excellent *in vivo* activity against sensitive and cisplatin-resistant leukemia L1210, as well as human non-small cell lung cancer A549 xenografts. Pharmacokinetic studies in rats showed that the high antitumor activity of the drug is due to controlled release of the active (dach)Pt(II) moiety. Another related platinum complex is:



301873¹: C66 H120 N21 O24 P3 Pt6

SOURCES – Il-Yang; Korea Institute of Science and Technology, Seoul (KR); Korea Research Institute of Chemical Technology, Taejeon (KR).

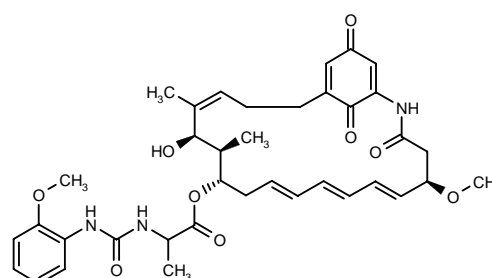
REFERENCES

1. Sohn, Y.S. et al. (Korea Institute of Science and Technology; Il-Yang Pharmaceutical Co., Ltd.) *Platinum complex conjugated to cyclotriphosphazene, its preparation, and anticancer agent comprising the same.* EP 1082331, US 6221906, WO 0058321.
2. Baek, H. et al. *Synthesis and antitumor activity of cyclotriphosphazene-(diamine)platinum (II) conjugates.* Anti-Cancer Drugs 2000, 11(9): 715.
3. Sohn, Y.S. et al. *Antitumor activity pharmacokinetics of a novel platinum(II)-cyclotriphosphazone conjugate drug KI60606.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2047.

ANTIBIOTICS AND ALKALOIDS

299377

2-(2-Methoxyphenylureido)propanoic acid (5*R*,6*E*,8*E*,10*E*,13*S*,14*R*,15*R*,16*Z*)-15-hydroxy-5-methoxy-14,16-dimethyl-3,22,24-trioxo-2-azabicyclo[18.3.1]tetracos-1(23),6,8,10,16,20-hexaen-13-yl ester



C37 H45 N3 O9; Mol wt: 675.7745

ACTION – Antineoplastic and antibacterial agent with low toxicity proven to inhibit the proliferation of rat kidney epithelial NRK cells transformed with human K-*ras* with an IC₅₀ value of 0.3 µM. *In vivo*, compound inhibited tumor growth in nude mice bearing human colon cancer HCT 116 solid tumors, giving a T/C x 100 value of 40 when given at 5 mg/kg/day i.p. x 10 days. A representative compound from a series of UCF-116 derivatives.

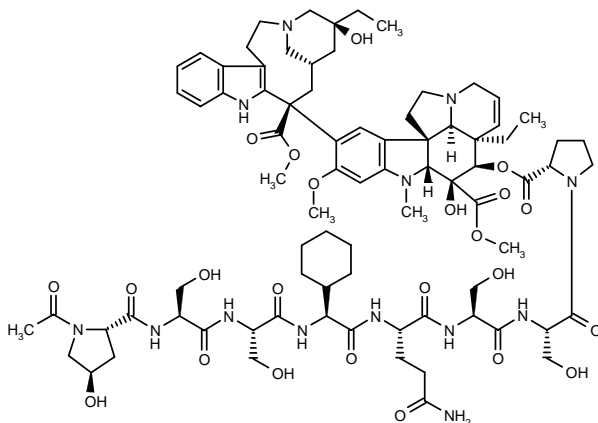
SOURCES – Kyowa Hakko; Lilly.

REFERENCES

1. Hara, M. et al. (Kyowa Hakko Kogyo Co., Ltd.; Eli Lilly and Company) *UCF116 derivs. as antitumor agents*. WO 0100583.

299600

(3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-[1-Acetyl-4(*R*)-hydroxy-L-prolyl-L-seryl-L-seryl-L-(2-cyclohexyl)glycyl-L-glutamyl-L-seryl-L-seryl-L-prolyloxy]-3a-ethyl-9-[5(*S*)-ethyl-5-hydroxy-9(*R*)-(methoxycarbonyl)-2,4,5,6,7(*S*),8,9,10-octahydro-1*H*-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylic acid methyl ester



C81 H113 N13 O23; Mol wt: 1636.8520

ACTION – A specifically claimed compound from a series of conjugates that comprise an oligopeptide having an amino acid sequence that is selectively proteolytically cleaved by free prostate-specific antigen (PSA) and a vinca alkaloid cytotoxic agent, potentially useful for the treatment of prostate cancer and benign prostatic hyperplasia.

SOURCE – Merck & Co.

REFERENCES

1. Brady, S.F. et al. (Merck & Co., Inc.) *Conjugates useful in the treatment of prostate cancer*. US 6174858.

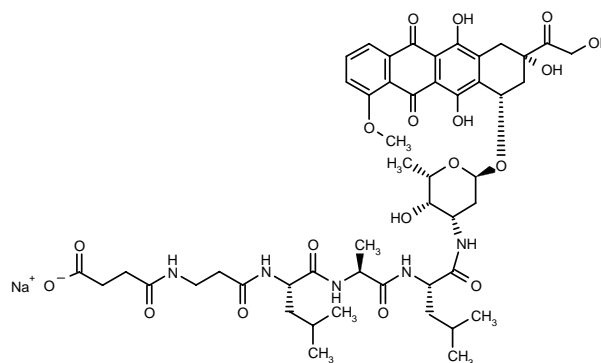
CPI-0004Na

257950

N-[*N*-(3-Carboxypropionyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]daunorubicin sodium salt

(8*S*,10*S*)-10-[3-[*N*-(3-Carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucylamido]-2,3,6-trideoxy-α-*L*-lyxo-hexopyranosyloxy]-8-(hydroxyacetyl)-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione sodium salt

Super-Leu-Dox
TAP-doxorubicin



C49 H64 N5 Na O18; Mol wt: 1034.0520

ACTION – Tetrapeptide prodrug of doxorubicin shown to be inactive against tumor cells *in vitro* (IC₅₀ > 50 µM) but to be selectively activated by proteolytic cleavage in the vicinity of the tumor, resulting in specific tumor cytotoxicity *in vivo*. Compound was stable in human whole blood. It prolonged survival of mice bearing doxorubicin-resistant colorectal carcinoma LS174T or breast cancer MX-1 and doxorubicin-sensitive prostate cancer LNCaP. In these models it was significantly more effective and better tolerated than doxorubicin.

SOURCE – Beckman Coulter.

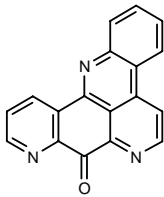
REFERENCES

1. Lobl, T.J. et al. (Beckman Coulter, Inc.) *Prodrug cpds. and process for preparation thereof*. WO 0033888.
2. Dubois, V. et al. *Pharmacokinetics and tissue distribution of CPI-004Na, a new prodrug of doxorubicin, in normal and tumor-bearing mice*. Proc Amer Assoc Cancer Res 2000, 41: Abstr 3329.
3. Gangwar, S. et al. *Synthesis of CPI-0004Na, a doxorubicin TAP prodrug*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abstr MEDI 223.
4. Nieder, M. et al. *Optimization of peptide prodrug structure with a cancer cell peptidase enzyme screen*. Proc Amer Assoc Cancer Res 2001, 42: Abstr 1757.
5. Pan, C. et al. *Cpi-0004, a doxorubicin prodrug that is inactive in vitro, prolongs survival of both doxorubicin-resistant and -sensitive human tumor-bearing mice*. Proc Amer Assoc Cancer Res 2001, 42: Abstr 1747.
6. Tabrizi-Fard, M. et al. *Evaluation of the pharmacokinetic properties of a doxorubicin prodrug in female ICR (CD-1) mice following intravenous bolus administration*. Proc Amer Assoc Cancer Res 2001, 42: Abstr 1746.
7. Trouet, A. et al. *CPI-0004Na: An extracellularly tumor-activated prodrug of doxorubicin*. Proc Amer Assoc Cancer Res 2000, 41: Abstr 3328.
8. *Company Profile: Coulter*. DailyDrugNews.com (Daily Essentials) 1997, Dec 1.

CRL-8299

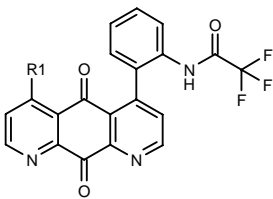
302086

8*H*-Benzo[*b*]pyrido[4,3,2-*de*]-1,7-phenanthrolin-8-one

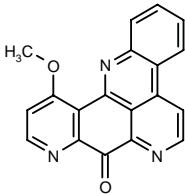


C18 H9 N3 O; Mol wt: 283.2891

ACTION – Antineoplastic agent, a synthetic analogue of the marine pyridoacridine alkaloid meridine with significantly improved *in vitro* cytotoxic activity against a panel of cancer cell lines (mean IC₅₀ = 2.2 and 170 nM, respectively). In mice bearing murine leukemia P388 and L1210 and mammary carcinoma MXT, compound significantly inhibited tumor growth and prolonged the survival of the mice. Other synthetic derivatives of meridine are:



Compound	R1	Formula
CRL-8275 [302293]	OMe	C ₂₁ H ₁₂ F ₃ N ₃ O ₄
CRL-8277 [302294]	H	C ₂₀ H ₁₀ F ₃ N ₃ O ₃



CRL-8276 [302292]: C19 H11 N3 O2

SOURCE – Lafon.

REFERENCES

1. Deflourne, E. et al. (Laboratoires L. Lafon) *Pharmaceutical compsn. based on polyaromatic cpds.* FR 2790954, WO 0055160.

2. Darro, F. et al. *Antitumor activities of synthetic analogues of meridine, a marine pyridoacridine alkaloid.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2616.

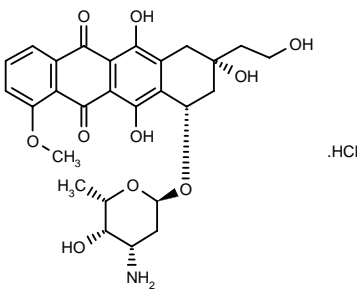
GPX-100*

273974

(8*R*,10*S*)-10-(3-Amino-2,3,6-trideoxy- α -L-galactopyranosyloxy)-6,8,11-trihydroxy-8-(2-hydroxyethyl)-1-methoxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione hydrochloride

(8*R*,10*S*)-10-(3-Amino-2,3,6-trideoxy- α -L-*lyxo*-hexopyranosyloxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyethyl)-1-methoxynaphthacene-5,12-dione hydrochloride

13-Deoxyadriamycin hydrochloride
13-Deoxydoxorubicin hydrochloride



C27 H31 N O10 . HCl; Mol wt: 565.9998

ACTION – Doxorubicin analogue, reported to have good antitumor activity in animals without the cardiotoxicity of the parent compound. A phase I study to determine the maximum tolerated dose showed no toxicity in patients receiving < 105 mg/m² by short i.v. infusion every 3 weeks; grade 1-2 nausea, vomiting, fatigue and anorexia were observed at higher doses, but there was no cardiotoxicity. The maximum tolerated dose of 140 mg/m² is recommended for phase II studies.

SOURCE – Gem Pharmaceuticals.

REFERENCES

1. Zhang, X. et al. (Gem Pharmaceuticals, Inc.) *13-Deoxyanthracycline derivs. and processes for preparing them.* EP 1011687, WO 9908687.

2. Busby, L. et al. *A phase I study of 13-deoxydoxorubicin (GPX-100) using accelerated dose titration.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4479.

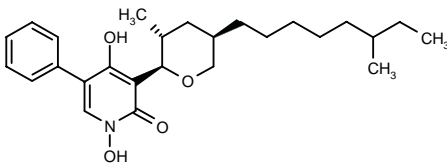
3. *Gem Pharmaceuticals seeks development partners for anticancer agent.* DailyDrugNews.com (Daily Essentials) 1998, June 3.

*Identified compound **273974** Drug Data Rep 1999, 021(05): 0450.

HEXAHYDRO-TMC-69

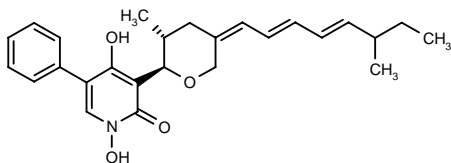
301973

1,4-Dihydroxy-3-[3(*R*)-methyl-5(*R*)-(6-methyloctyl)tetrahydro-2*H*-pyran-2(*R*)-yl]-5-phenylpyridin-2(1*H*)-one



C26 H37 N O4; Mol wt: 427.5813

ACTION – Antineoplastic agent, a derivative of the antitumor antibiotic **TMC-69**, isolated from a fermentation broth of *Chrysosporium* sp. TC1068. It showed cytotoxic activity against human colon carcinoma HCT 116 cells (IC_{50} = 0.8 μ M), murine melanoma B16 cells (IC_{50} = 1.9 μ M) and murine lymphoid neoplasm P388D1 (IC_{50} = 0.9 μ M). In addition, it exhibited inhibitory activity against Cdc25A phosphatase (IC_{50} = 3.1 μ M) and significant *in vivo* activity in B16 melanoma- or P388 leukemia-bearing mice.



TMC-69 [301974]: C₂₆ H₃₁ N O₄

SOURCE – Tanabe Seiyaku.

REFERENCES

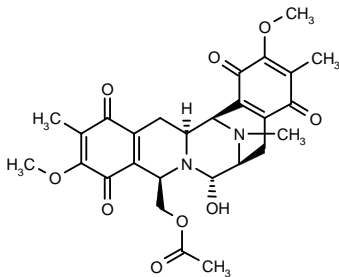
- Hirano, N. et al. *TMC-69, a new antitumor antibiotic with Cdc25A inhibitory activity, produced by Chrysosporium sp. TC1068. Taxonomy, fermentation and biological activities.* J Antibiot 2001, 54(5): 421.
- Kohno, J. et al. *Structure of TMC-69, a new antitumor antibiotic from Chrysosporium sp TC 1068.* Tetrahedron 2001, 57(9): 1731.
- Sugawara, K. et al. *Study on the synthesis of TMC-69 derivatives, cdc25A inhibitors.* 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)II-037.

JORUMYCIN

295997

Acetic acid [(1*R*,2*S*,10*R*,12*S*,13*S*)-12-hydroxy-7,18-dimethoxy-6,17,21-trimethyl-5,8,16,19-tetraoxo-11,21-diazapentacyclo[11.7.1.0^{2,11}.0^{4,9}.0^{15,20}]henicosa-4(9),6,15(20),17-tetraen-10-yl]methyl ester

(6*S*,7*S*,9*R*,14*aS*,15*R*)-9-(Acetoxymethyl)-6,7,9,14,14*a*,15-hexahydro-7-hydroxy-2,11-dimethoxy-3,12,16-trimethyl-,6,15-imino-4*H*-isoquino[3,2-*b*][3]-benzazocine-1,4,10,13(5*H*)-tetrone



C₂₇ H₃₀ N₂ O₉; Mol wt: 526.5390

ACTION – Cytotoxic alkaloid extracted from the marine nudibranch *Jorunna funebris*, a dimeric isoquinoline with strong cytotoxic activity against murine lymphoma P388, human lung carcinoma A549, human melanoma MEL-28 and human colon carcinoma HT-29 cells (IC_{50} = 12.5 ng/ml). In addition, compound showed antibacterial activity against various Gram-positive bacteria including *Bacillus subtilis* and *Staphylococcus aureus* at concentrations < 50 ng/ml.

SOURCE – Instituto Biomar.

REFERENCES

- Cimino, G. et al. (Instituto Biomar SA) *New active marine alkaloids.* WO 0119824.
- Fontana, A. et al. *A new antitumor isoquinoline alkaloid from the marine nudibranch Jorunna funebris.* Tetrahedron 2000, 56(37): 7305.

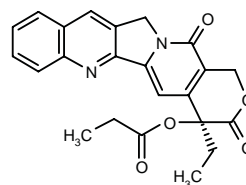
DNA-INTERCALATING DRUGS

CZ-48*

261782

4(*S*)-Ethyl-4-(propionyloxy)-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14-dione

20(*S*)-(Propionyloxy)camptothecin



C₂₃ H₂₀ N₂ O₅; Mol wt: 404.4200

ACTION – Antineoplastic agent, a propionate ester of camptothecin with improved resistance to lactone hydrolysis. *In vitro*, this prodrug was converted to an active camptothecin metabolite by tumor cells at different rates: high rates of metabolic conversion were found in melanoma and breast cancer cells, while much lower rates were found in colon cancer cells. *In vivo*, the prodrug was unaffected by plasma enzymes but was hydrolyzed by tissue esterases. Experiments in nude mice bearing human breast and lung cancer tumors demonstrated good activity and low toxicity compared to camptothecin.

SOURCE – Stehlin Foundation for Cancer Research, Houston, TX (US).

REFERENCES

- Cao, Z. and Giovanella, B.C. (The Stehlin Foundation for Cancer Research) *Derivs. of camptothecin and methods of treating cancer using these derivs.* US 5968943.
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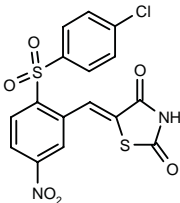
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ANTIMITOTIC DRUGS

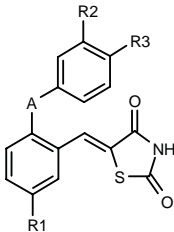
2999993

(Z)-5-[2-(4-Chlorophenylsulfonyl)-5-nitrobenzylidene]-thiazolidine-2,4-dione



C16 H9 Cl N2 O6 S2; Mol wt: 424.8401

ACTION – Antitumor agent, a telomerase inhibitor, as demonstrated *in vitro* by an IC₅₀ of 0.48 μM. In human renal carcinoma ACHN cells, the ratio of telomerase activity in treated cells versus enzyme activity in untreated cells was 16% at 10 μM. Other exemplified thiazolidine-dione derivatives include the following:



Compound	R1	R2	R3	A	Formula
299994	2-Pyr	H	Me	S	C ₂₂ H ₁₆ N ₂ O ₂ S ₂
299997	NO2	Cl	H	SO	C ₁₆ H ₉ ClN ₂ O ₅ S ₂

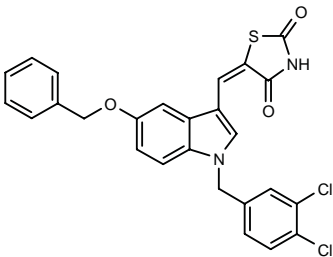
SOURCES – Geron; Kyowa Hakko.

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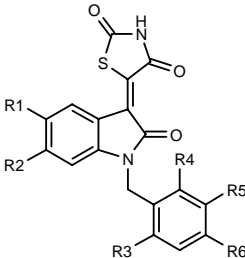
299999

(E)-5-[5-Benzyloxy-1-(3,4-dichlorobenzyl)-1*H*-indol-3-ylmethylene]thiazolidine-2,4-dione

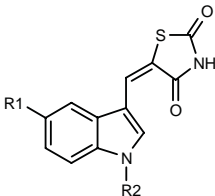


C26 H18 Cl2 N2 O3 S; Mol wt: 509.4112

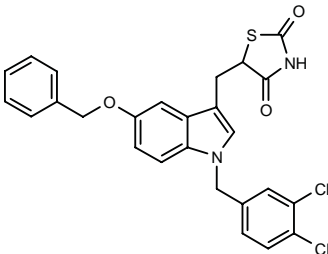
ACTION – Telomerase inhibitor, potentially useful for the treatment of telomerase-mediated conditions, particularly cancer. Other exemplified thiazolidinedione derivatives include the following:



Compound	R1	R2	R3=R4	R5=R6	Formula
300001	SO2NHPH	H	Cl	H	C ₂₄ H ₁₅ Cl ₂ N ₃ O ₅ S ₂
300003	H	COPh	H	Cl	C ₂₅ H ₁₄ Cl ₂ N ₂ O ₄ S
300004	4-(4-morpholinyl)-PhNHSO2	H	H	Cl	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₆ S ₂



Compound	R1	R2	Formula
300005	OCH2Ph	t-BuCO	C ₂₄ H ₂₂ N ₂ O ₄ S
300006	2,4-(MeO)2-PhNHCONH	3,4-(Cl)2-PhCH2	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₅ S
300007	OMe	4-(2,4-dioxo-thiazolidin-5-ylidene=CH)PhCH2	C ₂₄ H ₁₇ N ₃ O ₅ S ₂



300002: C26 H20 Cl2 N2 O3 S

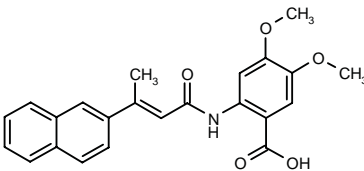
SOURCE – Geron.

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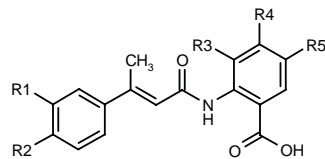
300493

4,5-Dimethoxy-2-[3-(2-naphthyl)-2(*E*)-butenamido]-benzoic acid



C23 H21 N O5; Mol wt: 391.4209

ACTION – Antineoplastic agent, a telomerase inhibitor (IC_{50} = 0.035 μ M) that is also useful for other telomerase-mediated conditions such as psoriasis and rheumatoid arthritis. Other exemplified carboxamides include the following:



Compound	R1	R2	R3	R4	R5	Formula
300494	Cl	Cl	H	H	H	C ₁₇ H ₁₃ Cl ₂ NO ₃
300495	Cl	Cl	H	Me	OMe	C ₁₉ H ₁₇ Cl ₂ NO ₄
300496	-CH=CHCH=CH-		H	H	H	C ₂₁ H ₁₇ NO ₃
300497	Cl	Cl	Me	H	Br	C ₁₈ H ₁₄ BrCl ₂ NO ₃
300498	-CH=CHCH=CH-		H	H	F	C ₂₁ H ₁₆ FNO ₃

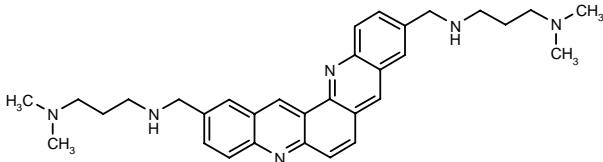
SOURCE – Boehringer Ingelheim.

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301010

N,N'-Bis[3-(dimethylamino)propyl]dibenzo[*b,j*]-1,7-phenanthroline-2,10-dimethanamine



C32 H40 N6; Mol wt: 508.7100

ACTION – Telomerase inhibitor (IC_{50} = 28 nM), a dibenzo-phenanthroline derivative found to stabilize the G-quadruplex, which is associated with inhibition of telomerase activity *in vitro*; its stabilizing effect was correlated with its affinity for the quadruplex structure, as well as with telomerase inhibition *in vitro*. Potentially useful as an anticancer agent.

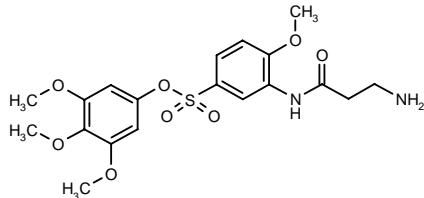
SOURCE – CNRS.

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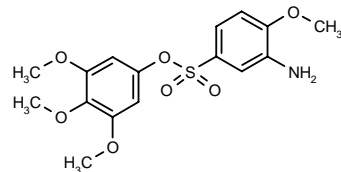
301977

3-(3-Aminopropionamido)-4-methoxybenzenesulfonic acid 3,4,5-trimethoxyphenyl ester



C19 H24 N2 O8 S; Mol wt: 440.4706

ACTION – Antimitotic agent, a prodrug of the sulfonate analogue of combretastatin A-4 [298297] with an improved pharmacokinetic profile and 100% oral bioavailability after a dose of 10 mg/kg in rats. The active compound showed potent antiproliferative activity against human lung carcinoma NCI-H460 and multidrug-resistant human colon carcinoma HCT-15 cells (IC_{50} = 2.7 and 4.1 nM, respectively), and it also inhibited tubulin polymerization (IC_{50} = 6.7 μ M) and competed for the colchicine binding site.



298297: C16 H19 N O7 S

SOURCE – Abbott.

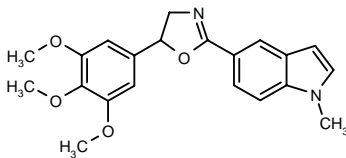
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301979

1-Methyl-5-[5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-oxazol-2-yl]-1*H*-indole



C21 H22 N2 O4; Mol wt: 366.4148

ACTION – Antimitotic agent (IC_{50} = 6.75 μ M for inhibition of tubulin polymerization) with potent antiproliferative activity against human lung carcinoma NCI-H460 and multidrug-resistant human colon carcinoma HCT-15 cells (IC_{50} = 34 and 20 nM, respectively). Despite relatively low drug exposure after oral administration (F = 35, 30, 8 and 28%, respectively, in rats, mice, dogs and monkeys), it showed good *in vivo* efficacy against ovarian sarcoma M5076 in mice, where it significantly extended survival time (% ILS > 200 at 50 mg/kg/day p.o.) whereas the parent compound A-105972, paclitaxel and vincristine showed little or no activity.

SOURCE – Abbott.

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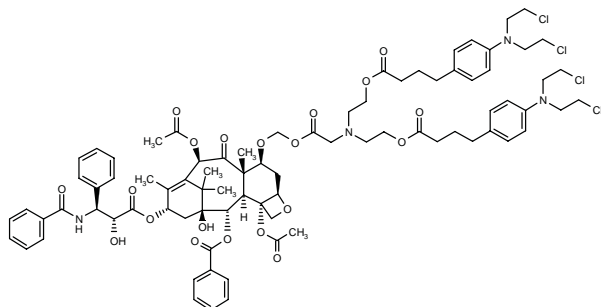
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302655

[2a*R*,4*S*,4a*S*,6*R*,9*S*(2*R*,3*S*),11*S*,12*S*,12a*R*,12b*S*]-6,12b-Diacetoxy-9-(3-benzamido-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-4-[2-[*N,N*-bis[2-[4-[4-[*N,N*-bis(2-chloroethyl)amino]phenyl]butyryloxy]ethyl]-amino]acetoxymethoxy]-11-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benzo[1,2-*b*]-oxet-5-one



C82 H98 Cl4 N4 O20; Mol wt: 1601.4960

ACTION – Paclitaxel–chlorambucil hybrid shown to be inactive in a cell-free tubulin polymerization assay but very potent in inhibiting the proliferation of human colon carcinoma HCT 116 cells ($IC_{50} = 24$ nM). *In vivo*, compound showed excellent activity against paclitaxel- and chlorambucil-sensitive, and paclitaxel-resistant, chlorambucil-sensitive Madison murine lung carcinoma M109. In these models it was superior to paclitaxel or chlorambucil alone or the optimal combination of both agents. Activity was also seen against paclitaxel-sensitive, chlorambucil-resistant human ovarian carcinoma A2780 xenografts and paclitaxel-insensitive, chlorambucil-sensitive murine sarcoma M5076, demonstrating that it retains both paclitaxel- and chlorambucil-like activity. No activity was seen against human ovarian carcinoma HCT/pk xenografts resistant to both paclitaxel and chlorambucil. Potentially useful for extending the therapeutic utility of paclitaxel against resistant or paclitaxel-insensitive tumors.

SOURCE – Bristol-Myers Squibb.

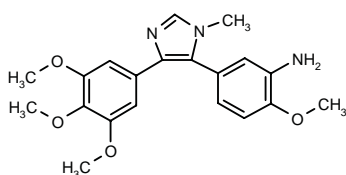
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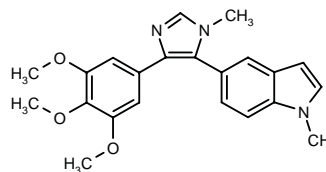
300873

2-Methoxy-5-[4-(3,4,5-trimethoxyphenyl)-1-methyl-1*H*-imidazol-5-yl]phenylamine



C20 H23 N3 O4; Mol wt: 369.4187

ACTION – Potent, orally active combretastatin A-4 analogue with submicromolar cytotoxicity against human non-small cell lung carcinoma NCI-H460 cells and human colon adenocarcinoma HCT-15 cells ($IC_{50} = 0.17$ and 0.22 μ M, respectively), and favorable oral pharmacokinetics in rats, mice, dogs and monkeys ($F = 87, 89.7, 48.8$ and 91.2% , respectively). Moreover compound exhibited good oral efficacy against murine ovarian sarcoma M5076 tumors giving complete tumor remission at a dose of 30 mg/kg/day for 27 days. Another combretastatin A-4 analogue is:



302036: C22 H23 N3 O3

SOURCE – Abbott.

REFERENCES

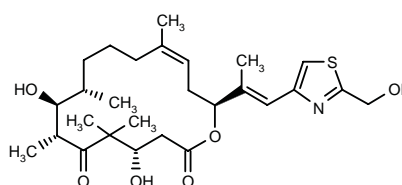
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DEOXYEPOTHILONE F

296536

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[(*E*)-1-methyl-2-[2-(hydroxymethyl)-4-thiazolyl]ethenyl]-1-oxacyclohexadec-13-ene-2,6-dione

12,13-Deoxyepothilone F
21-Hydroxyepothilone D
dEpoF



C27 H41 N O6 S; Mol wt: 507.6879

ACTION – Antineoplastic agent, an epothilone analogue that competes with paclitaxel for microtubule binding but, unlike paclitaxel, retains remarkable potency against multidrug-resistant tumor cells. Compound exhibited cytotoxic activity comparable to paclitaxel against sensitive tumor cell lines ($CC_{50} = 0.0095$ and 0.0021 μ M, respectively, against human leukemia CEM cells), but showed very low crossresistance in multidrug-resistant CEM cells compared with paclitaxel (1.8x and 1,971x, respectively). *In vivo* compound induced complete remission of human leukemia K562 and human breast cancer MX-1 xenografts in mice. Moreover, it showed highly improved aqueous solubility compared to paclitaxel, making it a promising candidate for cancer chemotherapy.

SOURCE – Sloan-Kettering Institute, New York, NY (US).

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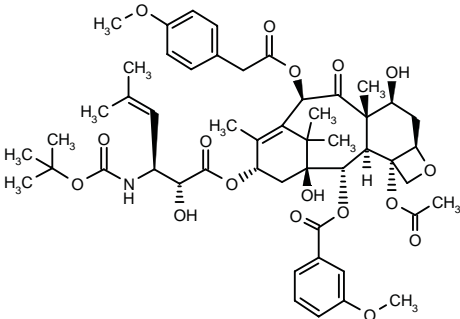
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SB-T-12130301

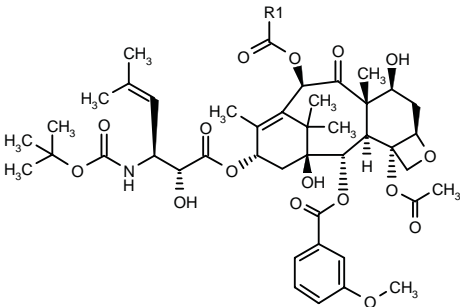
301967

3-Methoxybenzoic acid (2*aR*,4*S*,4*aS*,6*R*,9*S*,11*S*,12*S*,12*aR*,12*bS*)-12*b*-acetoxy-9-[3(*S*)-(*tert*-butoxycarbox-amido)-2(*R*)-hydroxy-5-methyl-4-hexenoyloxy]-4,11-dihydroxy-6-[2-(4-methoxyphenyl)acetoxy]-4*a*,8,13,13-tetramethyl-5-oxo-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benzo-[1,2-*b*]oxet-12-yl ester



C51 H65 N O17; Mol wt: 964.0645

ACTION – Second-generation taxoid with improved activity compared to paclitaxel and docetaxel against both sensitive and multidrug-resistant human breast carcinoma LCC6 (IC₅₀ = 0.39 and 0.4 nM, respectively) and MCF-7 cells (IC₅₀ = 0.6 and 1.84 nM, respectively). Other related compounds are:



Compound	R1	Formula
SB-T-121303201 [301968]	2-MeO-Ph	C ₅₀ H ₆₃ NO ₁₇
SB-T-121303311 [301969]	OCH2Ph	C ₅₀ H ₆₃ NO ₁₇

SOURCES – Roswell Park Cancer Institute, Buffalo, NY (US); State University of New York, Stony Brook, Stony Brook, NY (US).

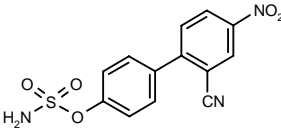
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HORMONAL AGENTS

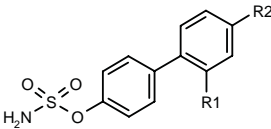
300014

Sulfamic acid 2'-cyano-4'-nitrobiphenyl-4-yl ester

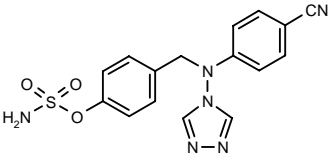


C13 H9 N3 O5 S; Mol wt: 319.2961

ACTION – Steroid sulfatase inhibitor proven to inhibit the activity of this enzyme *in vitro* by 87% at 3 nM in human breast cancer MCF-7 cells and *in vivo* by 99.5% in the liver and by 100% in the uterus at an oral dose of 0.5 mg/kg in female rats. Potentially useful for the treatment of estrogen-related diseases such as breast, uterine and ovarian cancers, endometriosis, adenomyosis uteri, mastopathy, male gynecomastia, benign prostatic hyperplasia and male infertility due to oligospermia. Other exemplified phenyl sulfamate derivatives include the following:



Compound	R1	R2	Formula
300015	NO2	H	C ₁₂ H ₁₀ N ₂ O ₅ S
300016	CN	H	C ₁₃ H ₁₀ N ₂ O ₅ S
300017	H	NO2	C ₁₂ H ₁₀ N ₂ O ₅ S
300018	H	OSO2NH2	C ₁₂ H ₁₂ N ₂ O ₆ S ₂
300019	NO2	NO2	C ₁₂ H ₉ N ₃ O ₇ S
300020	CN	CN	C ₁₄ H ₉ N ₃ O ₅ S



300021: C16 H14 N6 O3 S

SOURCE – Teikoku Hormone.

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CANCER IMMUNOTHERAPY

MELACINE®+

188539

Melanoma vaccine which consists of an allogeneic melanoma lysate and the adjuvant Detox™ (mono-phosphoryl lipid A)

ACTION – Melanoma therapeutic vaccine

INDICATION – Treatment of stage IV melanoma

PRESENTATION – Powder for intramuscular injection, 500 µg cell wall skeleton, 20 x 10⁶ cells melanoma lysate and 50 µg monophosphoryl lipid A.

SOURCES – Corixa; marketed by Schering-Plough.

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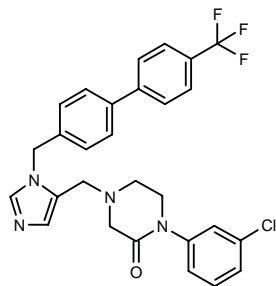
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*Drug Data Rep 1993, 015(03): 0290.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

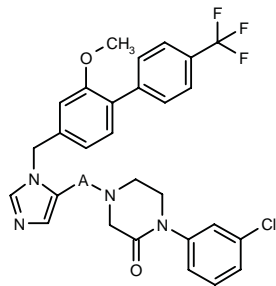
298696

1-(3-Chlorophenyl)-4-[1-[4'-(trifluoromethyl)biphenyl-4-ylmethyl]-1*H*-imidazol-5-ylmethyl]piperazin-2-one



C28 H24 Cl F3 N4 O; Mol wt: 524.9716

ACTION – Dual inhibitor of protein farnesyltransferase and protein geranylgeranyltransferase type I (IC₅₀ = 5.7 and 140 nM, respectively) with good oral pharmacokinetics in dogs (half-life = 5 h; C_{max} = 0.18 μM). Potentially useful as an antineoplastic agent. Other related biaryl compounds are:



Compound	A	Formula
298710	-(CH2)2-	C ₃₀ H ₂₈ ClF ₃ N ₄ O ₂
298711	-CH2-	C ₂₉ H ₂₆ ClF ₃ N ₄ O ₂

SOURCE – Merck & Co.

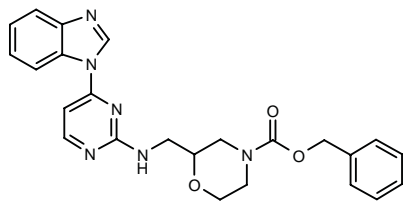
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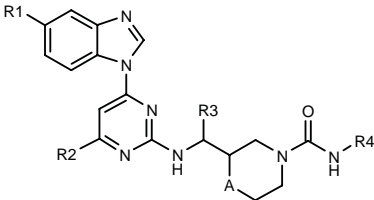
299574

2-[4-(1*H*-Benzimidazol-1-yl)pyrimidin-2-ylaminomethyl]-morpholine-4-carboxylic acid benzyl ester



C24 H24 N6 O3; Mol wt: 444.4926

ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, Fyn(B), Fyn(T), Lyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment and prevention of protein tyrosine kinase-associated disorders such as immune diseases and hyperproliferative disorders. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
299576	H	H	H	1-Naph	O	C ₂₇ H ₂₅ N ₇ O ₂
299582	H	H	Me	1-Naph	O	C ₂₈ H ₂₇ N ₇ O ₂
299584	3-pyridazinyl	H	Me	1-Naph	N(Me)	C ₃₃ H ₃₂ N ₁₀ O
299585	6-N(Me)2-3-pyridazinyl	H	Me	1-Naph	N(Me)	C ₃₅ H ₃₇ N ₁₁ O
299587	2-NH2-4-pyrimidinyl	H	Me	Ph	N(Me)	C ₂₉ H ₃₁ N ₁₁ O
299588	2-NH2-4-pyrimidinyl	2-(CH2OH)-Ph	Me	Ph	N(Me)	C ₃₆ H ₃₇ N ₁₁ O ₂

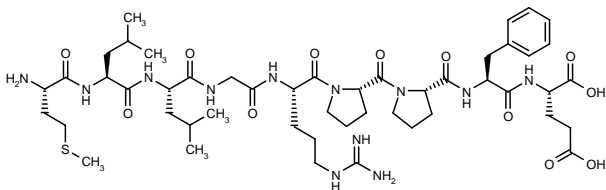
SOURCE – Merck & Co.

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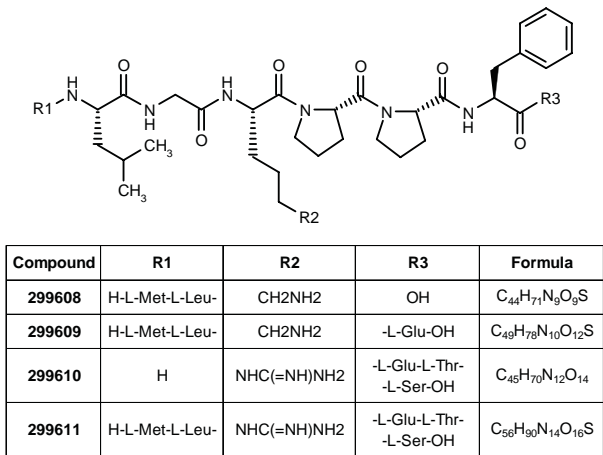
299607

L-Methionyl-L-leucyl-L-leucyl-glycyl-L-arginyl-L-prolyl-L-prolyl-L-phenylalanyl-L-glutamic acid



C49 H78 N12 O12 S; Mol wt: 1059.2930

ACTION – A representative compound from a series of short peptide derivatives of the HJ loop of serine/threonine kinases such as Raf and Polo, potentially useful for modulating the activity of serine/threonine kinases and thus for the treatment of a wide range of diseases such as cancer, obesity, CNS disorders, autoimmune disorders, inflammation, cardiovascular disorders and type 2 diabetes. *In vitro*, compound was found to significantly inhibit the proliferation of bovine aortic cells and murine transformed SVR cells at a concentration of 10 μM. Other specifically claimed peptides are:



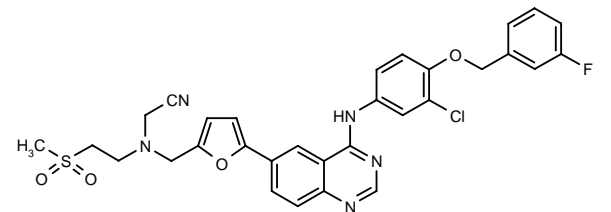
SOURCES – Children’s Medical Center, Boston, MA (US); Yissum.

REFERENCES

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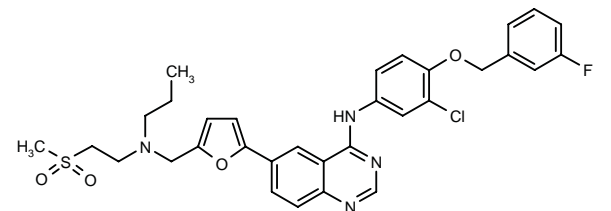
300091

2-[N-[5-[4-[3-Chloro-4-(3-fluorobenzyloxy)phenylamino]-quinazolin-6-yl]furan-2-ylmethyl]-N-[2-(methylsulfonyl)-ethyl]amino]acetonitrile



C31 H27 Cl F N5 O4 S; Mol wt: 620.1023

ACTION – Agent for the treatment of cancer or psoriasis, an inhibitor of epidermal growth factor (EGF) receptor, c-erbB-2 and c-erbB-4 protein tyrosine kinases (IC₅₀ < 0.10 μM). Compound was further shown to inhibit the proliferation of human breast carcinoma BT-474, head and neck tumor HN5 and gastric carcinoma N87 cell lines with IC₅₀ values < 0.10 μM. Another exemplified compound from this series of quinazoline and pyridopyrimidine derivatives is:



300092: C32 H32 Cl F N4 O4 S

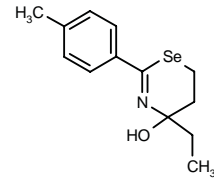
SOURCE – GlaxoSmithKline.

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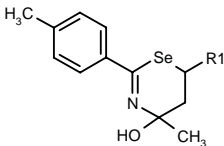
300178

4-Ethyl-2-(4-methylphenyl)-5,6-dihydro-4*H*-1,3-selenazin-4-ol



C13 H17 N O Se; Mol wt: 282.2433

ACTION – Antineoplastic agent, a protein kinase inhibitor that acts by selectively inhibiting calcium-dependent calmodulin kinase III (CaMKIII) over other kinases, as demonstrated by IC₅₀ values of 2.6 and 140 μM against CaMKIII and protein kinase C, respectively. In addition, compound was shown to inhibit the proliferation of human fibrosarcoma HT-1080, pancreatic cancer Aspc-1, colon carcinoma HCT 116, breast cancer MCF-7 and breast cancer MDA-MB-231 cells with IC₅₀ values of 7.76, 5.5, 0.4, 0.8 and 4.3 μM, respectively. Other exemplified compounds from this series of 1,3-selenazil-4-ol derivatives include the following:



Compound	R1	Formula
300179	i-Pr	C ₁₅ H ₂₁ NOSe
300180	Pr	C ₁₅ H ₂₁ NOSe

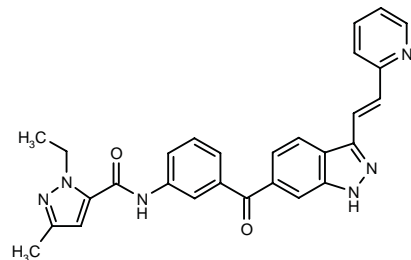
SOURCE – Nippon Kayaku.

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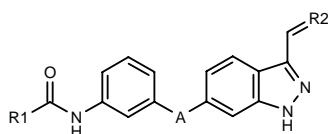
300189

1-Ethyl-3-methyl-N-[3-[3-[(*E*)-2-(2-pyridinyl)vinyl]-1*H*-indazol-6-ylcarbonyl]phenyl]-1*H*-pyrazole-5-carboxamide

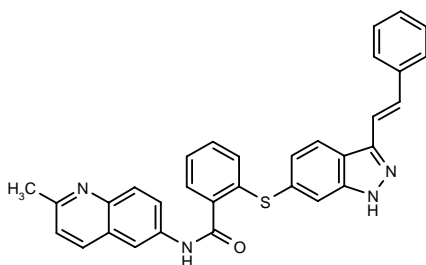


C28 H24 N6 O2; Mol wt: 476.5376

ACTION – An inhibitor of protein kinases with selectivity for vascular endothelial growth factor (VEGF) receptor ($K_i = 0.03 \mu\text{M}$) over other kinases such as LCK, CHK, FGF (fibroblast growth factor), CDK2 and CDK4. Compound was shown to inhibit VEGF-induced proliferation of human umbilical vein endothelial cells (HUVEC) in the absence or presence of albumin ($\text{IC}_{50} = 0.48$ and $4.4 \mu\text{M}$, respectively). In addition, it was active in an *in vivo* model of retinal vascular development in neonatal rats, giving 64% inhibition when injected into the eye at a concentration of 10 mg/ml. Potentially useful in the treatment of diseases mediated by kinase activity such as cancer, as well as other disease states associated with unwanted angiogenesis and/or cellular proliferation such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis and psoriasis. Other exemplified compounds from this series of indazole derivatives include the following:



Compound	R1	R2	A	Formula
300190	3-Ac-Ph	1,3-benzodioxol-5-yl-CH=	N(Me)	$\text{C}_{32}\text{H}_{26}\text{N}_4\text{O}_4$
300191	Ph	2-Pyr-CH=	O	$\text{C}_{27}\text{H}_{20}\text{N}_4\text{O}_2$
300193	CH=CHMe	2-Pyr-CH=	CO	$\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_2$
300194	4-indolyl	2-Pyr-CH=	CO	$\text{C}_{30}\text{H}_{21}\text{N}_5\text{O}_2$
300195	Ph	2-Pyr-CH=	CO	$\text{C}_{28}\text{H}_{20}\text{N}_4\text{O}_2$
300196	Ph	1-pyrrolyl-N=	CO	$\text{C}_{26}\text{H}_{19}\text{N}_5\text{O}_2$



300192: $\text{C}_{32}\text{H}_{24}\text{N}_4\text{O}_5$

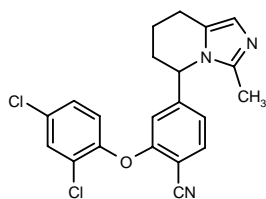
SOURCE – Agouron (Pfizer).

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- Kania, R.S. et al. (Agouron Pharmaceuticals, Inc.) *Indazole cpds. and pharmaceutical compns. for inhibiting protein kinases, and methods for their use*. WO 0102369.

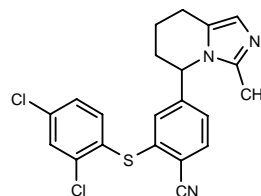
300487

2-(2,4-Dichlorophenoxy)-4-(3-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile



$\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}$; Mol wt: 398.2913

ACTION – An inhibitor of protein prenyltransferase and the prenylation of the oncogene protein Ras, claimed to be useful for the treatment of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease. Another compound from this series of tetrahydroimidazopyridine and tetrahydroisoquinoline derivatives is:



300488: $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{N}_3\text{S}$

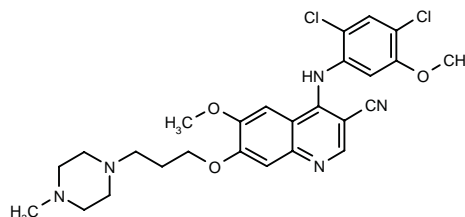
SOURCE – Merck & Co.

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301966

4-(2,4-Dichloro-5-methoxyphenylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile



$\text{C}_{26}\text{H}_{29}\text{Cl}_2\text{N}_5\text{O}_3$; Mol wt: 530.4531

ACTION – Potent and selective Src protein tyrosine kinase inhibitor with respective IC_{50} values of 1.2 and 100 nM in an enzymatic assay and an Src-dependent cell proliferation assay in Src-transformed fibroblasts. *In vivo*, compound (25 mg/kg i.p. twice a day for 10 days) induced significant inhibition of tumor growth in nude mice inoculated with Src-transformed fibroblasts. Potentially useful as an antineoplastic agent and also for the treatment of Src-dependent diseases such as osteoporosis and stroke.

SOURCE – Wyeth-Ayerst.

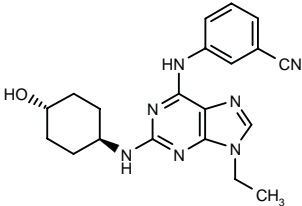
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CGP-79807

287728

trans-3-[9-Ethyl-2-(4-hydroxycyclohexylamino)-9H-purin-6-ylamino]benzonitrile



C20 H23 N7 O; Mol wt: 377.4497

ACTION – Potent and selective dual CDK1 and CDK2 inhibitor (IC₅₀ = 0.028 and 0.046 μM, respectively) that is able to inhibit phosphorylation of retinoblastoma protein (pRb) in T98G cells at 1.5 μM and to inhibit the growth of a series of cancer cell lines including human non-small cell lung carcinoma NCI-H596, epidermal growth factor (EGF) receptor-overexpressing human breast carcinoma MDA-MB-468, human prostate carcinoma DU 145, human osteogenic sarcoma Saos-2 and human bladder carcinoma T24 (IC₅₀ = 0.36, 1.9, 0.52, 0.55 and 0.41 μM, respectively). Compound arrested glioblastoma T98G cells in the G2/M phase and subsequently induced apoptosis. *In vivo*, it was well absorbed in mice, with peak plasma and tumor levels exceeding 10 μM after a dose of 100 mg/kg p.o. In a hollow fiber model in mice using KB31 cells, a dose of 50 mg/kg p.o. b.i.d. produced complete cell cycle arrest, with no growth recovery of tumor cells at 5 days after treatment.

SOURCE – Novartis.

REFERENCES

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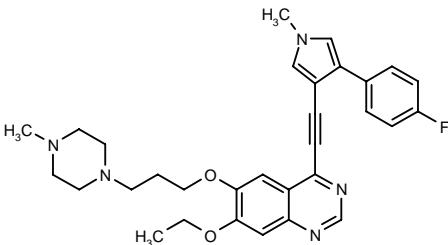
2. Ruetz, S. et al. *Effect of CGP79807 on cell cycle dependent kinases (CDK) cell cycle progression and onset of apoptosis in in-vitro and well in-vivo models*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3570.

3. St Ruetz, R. et al. *Demonstration of in vivo efficacy of CGP79807 on cell cycle dependent kinases (CDK), cycle progression and onset of apoptosis in a hollow-fiber model in mice*. Proc Amer Assoc Cancer Res 2001, 42: Abst 4872.

DAB-1059

302096

7-Ethoxy-4-[2-[4-(4-fluorophenyl)-1-methyl-1H-pyrrol-3-yl]-ethynyl]-6-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline



C31 H34 F N5 O2; Mol wt: 527.6406

ACTION – Potent epidermal growth factor (EGF) receptor tyrosine kinase inhibitor (IC₅₀ = 7 nM) with antitumor activity in mice bearing human epidermoid carcinoma A-431 xenografts.

SOURCES – Mitsubishi-Tokyo Pharmaceuticals; Osaka University, Osaka (JP).

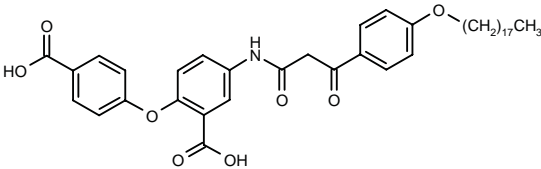
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ANGIOGENESIS INHIBITORS

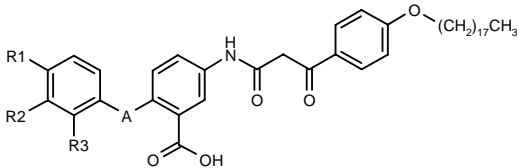
299699

2-(4-Carboxyphenoxy)-5-[3-[4-(octadecyloxy)phenyl]-3-oxopropionamido]benzoic acid



C41 H53 N O8; Mol wt: 687.8687

ACTION – Vascular endothelial growth factor (VEGF) receptor antagonist, as demonstrated by IC₅₀ values of 0.44 and 0.18 μM for inhibition of the binding of [¹²⁵I]-VEGF in Flt-1- and KDR-expressing NIH3T3 cells, respectively. In addition, compound was shown to inhibit the growth of human colon carcinoma Col-1 tumors implanted s.c. in nude mice, giving a T/C x 100 value of 29.9% at 50 mg/kg/day i.p. x 28 days. Potentially useful for the treatment of VEGF-mediated neovascularization disorders such as diabetic retinopathy, chronic rheumatoid arthritis and cancer, as well as for the treatment of VEGF-mediated disorders of vascular permeability such as cerebral edema in ischemia–reperfusion disorders. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
299700	H	CO2H	H	O	C ₄₁ H ₅₃ NO ₈
299701	H	H	CO2H	O	C ₄₁ H ₅₃ NO ₈
299702	CO2H	H	H	S	C ₄₁ H ₅₃ NO ₇ S
299703	H	CO2H	H	S	C ₄₁ H ₅₃ NO ₇ S
299704	CO2H	H	H	NH	C ₄₁ H ₅₄ N ₂ O ₇
299705	H	CO2H	H	NH	C ₄₁ H ₅₄ N ₂ O ₇

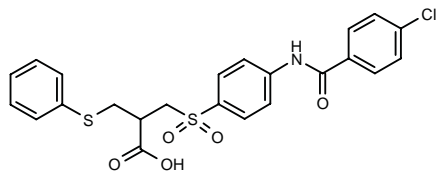
SOURCE – Taisho.

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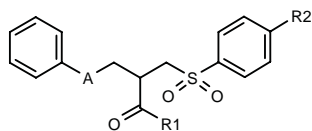
300309

3-[4-(4-Chlorobenzamido)phenylsulfonyl]-2-(phenyl-sulfonylmethyl)propionic acid



C23 H20 Cl N O5 S2; Mol wt: 489.9980

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as the gelatinases (MMP-2), the membrane-type MMP involved in gelatinase activation (MMP-4), the stromelysins (MMP-3 and MMP-10), collagenase 3 (MMP-13) and neutrophil collagenase (MMP-8), with selectivity over fibroblast collagenase (MMP-1), as demonstrated by K_i values of 1.4 and 50,560 nM, respectively, against human MMP-2 and MMP-1. Potentially useful for the treatment or prevention of tumor growth and metastasis, rheumatoid arthritis, osteoarthritis, ophthalmic diseases, cardiovascular diseases, periodontal disease, multiple sclerosis and Alzheimer’s disease. Other compounds from this series of 3-arylsulfonyl-2-(substituted methyl)propanoic acid derivatives include the following:



Compound	R1	R2	A	Formula
300310	OH	NHCOPh	S	C ₂₃ H ₂₁ NO ₅ S ₂
300311	NHOH	4-Cl-Ph	S	C ₂₂ H ₂₀ ClNO ₄ S ₂
300312	OH	4-Cl-PhCONH	O	C ₂₃ H ₂₀ ClNO ₆ S

SOURCE – Pharmacia.

REFERENCES

1. Mantegani, S. et al. (Pharmacia & Upjohn SpA) *3-Arylsulfonyl-2-(subst. methyl)propanoic acid derivates as matrix metalloproteinase inhibitors*. WO 0105756.

ANGINEX

301151

L-Alanyl-L-asparaginyL-L-isoleucyl-L-lysyl-L-leucyl-L-seryl-L-valyl-L-glutaminyL-L-methionyl-L-lysyl-L-leucyl-L-phenylalanyl-L-lysyl-L-arginyL-L-histidyl-L-leucyl-L-lysyl-L-tryptophyl-L-lysyl-L-isoleucyl-L-isoleucyl-L-valyl-L-lysyl-L-leucyl-L-asparaginyL-L-aspartyl-glycyl-L-arginyL-L-glutamyl-L-leucyl-L-seryl-L-leucyl-L-aspartic acid

βpep25

C180 H305 N51 O45 S; Mol wt: 3935.7680

ACTION – Angiogenesis inhibitor, a β-sheet-forming peptide able to inhibit proliferation and induce apoptosis in vascular endothelial cells, as well as to inhibit endothelial cell adhesion and migration on the extracellular matrix. *In vivo*, compound was found to inhibit the growth of human ovarian carcinoma MA-148 xenografts in nude mice after both local and systemic (via osmotic minipump) administration. In this model, tumor growth inhibition was correlated with a reduction in vessel density and increase in apoptosis in the tumors. No toxicity or behavioral changes were observed. Potentially useful for the treatment of various pathological conditions dependent on excessive angiogenesis such as tumor growth, rheumatoid arthritis, restenosis and diabetic retinopathy.

SOURCES – Universiteit Maastricht, Maastricht (NL); University of Minnesota, Minneapolis, MN (US).

REFERENCES

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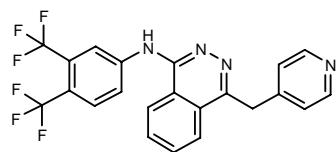
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NVP-ADD-777/ZK-202664

302314

N-[3,4-Bis(trifluoromethyl)phenyl]-4-(pyridin-4-ylmethyl)-phthalazin-1-amine



C22 H14 F6 N4; Mol wt: 448.3686

ACTION – Antiangiogenic agent, a vascular endothelial growth factor (VEGF) kinase inhibitor, proven to selectively inhibit the KDR receptor tyrosine kinase (IC₅₀ = 0.5 μM) without affecting fibroblast growth factor (FGF) receptor kinases (IC₅₀ > 10 μM). Consistent with these results, compound inhibited the proliferation of human umbilical vein endothelial cells (HUVEC) induced by VEGF (EC₅₀ = 0.02 μM) but not by bFGF (EC₅₀ > 1 μM). However, *in vivo* in growth factor-induced angiogenesis models in mice, compound was found to inhibit both VEGF- and bFGF-mediated angiogenesis with respective ED₅₀ values of 6 and 23 mg/kg/day. Potential anti-neoplastic agent.

SOURCES – Novartis; Schering AG.

REFERENCES

1. Bold, G. et al. (Novartis AG) *Phthalazine derivs. for treating inflammatory diseases*. WO 0059509.

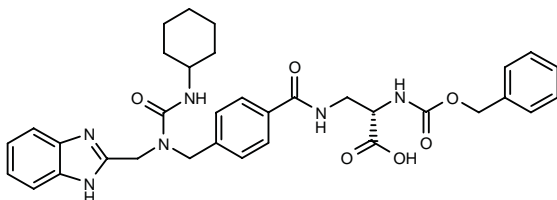
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SCH-221153*

290755

3-[4-[1-(1*H*-Benzimidazol-2-ylmethyl)-3-cyclohexylureidomethyl]benzamido]-2(*S*)-(benzyloxycarbonyl-amino)propionic acid

3-[4-[1-(1*H*-Benzimidazol-2-ylmethyl)-3-cyclohexylureido-methyl]benzamido]-*N*-(benzyloxycarbonyl)-L-alanine



C34 H38 N6 O6; Mol wt: 626.7102

ACTION – Antineoplastic agent, a dual antagonist of integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptors (IC_{50} = 3.2 and 1.7 nM, respectively, for inhibition of echistatin binding) with high selectivity over related $\alpha_{IIb}\beta_3$ and $\alpha_5\beta_1$ receptors (IC_{50} = 1294 and 421 nM, respectively). This activity was also demonstrated in cell-based assays where compound inhibited the binding of echistatin to $\alpha_v\beta_3$ and $\alpha_v\beta_5$ -expressing HEK-293 cells and inhibited cell proliferation induced by fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor (VEGF) with IC_{50} values of 3-10 μ M. Compound inhibited angiogenesis induced by FGF2 in the chick chorioallantoic membrane assay (IC_{50} = 100 ng/implant) and also significantly inhibited the growth of human melanoma LOX tumors implanted into SCID mice either intradermally or s.c., giving about 70% inhibition of tumor growth at a dose of 20 mg/kg i.p. twice daily for 15 days.

SOURCE – Schering-Plough.

REFERENCES

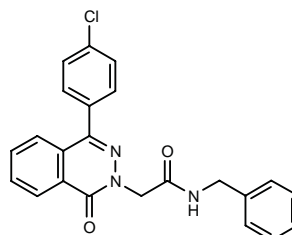
1. Neustadt, B.R. and Smith, E.M. (Schering Corp.) *Benzimidazole cpds. that are vitronectin receptor antagonists*. US 6204282.
2. Neustadt, B.R. and Smith, E.M. (Schering Corp.) *Benzimidazole cpds. that are vitronectin receptor antagonists*. WO 0032578.
3. Kumar, C.C. et al. *Inhibition of angiogenesis and tumor growth by SCH221153, a dual $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptor antagonist*. Cancer Res 2001, 61(5): 2232.
4. Yin, Z. et al. *Inhibition of angiogenesis and tumor growth by SCH221153, a dual $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptor antagonist*. Proc Amer Assoc Cancer Res 2001, 42: Abst 429.

*Identified compound **290755** (see **290750**) Drug Data Rep 2000, 022(10): 0944.

OTHER ONCOLYTIC DRUGS

299735

N-Benzyl-2-[4-(4-chlorophenyl)-1-oxo-1,2-dihydrophthalazin-2-yl]acetamide



C23 H18 Cl N3 O2; Mol wt: 403.8672

ACTION – Agent that selectively induces or promotes apoptosis in neoplastic cells, with potential for the treatment of neoplasia, including precancerous and cancerous lesions. *In vitro*, compound was shown to inhibit the growth of human colon carcinoma SW480 cells (IC_{50} = 5.18 μ M) and to induce apoptosis in these cells, as determined in a DNA fragmentation assay (EC_{50} = 7.19 μ M). A representative compound from a series of [4,5]-fused-1,3-disubstituted-1,2-diazine-6-one derivatives.

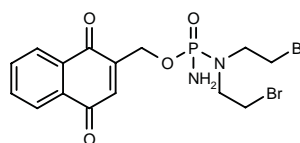
SOURCE – Cell Pathways.

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1. Wang, X. et al. (Cell Pathways, Inc.) *[4,5]-Fused-1,3-disubstd.-1,2-diazine-6-one derivs. with nitrogen containing substituents in position one for the treatment of neoplasia*. US 6180629.

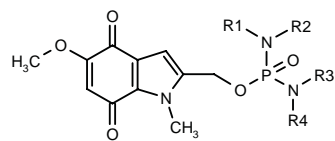
300110

N,N-Bis(2-bromoethyl)diamidophosphoric acid (1,4-dioxo-1,4-dihydronaphthalen-2-ylmethyl) ester

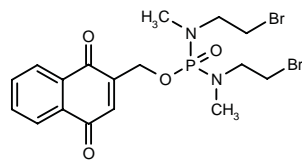


C15 H17 Br2 N2 O4 P; Mol wt: 480.0913

ACTION – Antineoplastic agent that acts as a prodrug of a highly cytotoxic agent and is designed to be selectively activated by enzymes that are overexpressed in cancer cells, thus reducing the incidence of side effects. *In vitro*, compound exhibited cytotoxicity in the low micromolar range against a series of human tumor cell lines; for example, against HT-29 and BE cells, compound exhibited IC_{50} values of 7.8 and 4.6 μ M, respectively. When compound was tested *in vivo* in nude mice bearing human kidney carcinoma A4982LM xenografts, it exhibited 40% inhibition of tumor growth on day 38 after a single dose of 25 mg/kg s.c. Other exemplified compounds from this series of phosphoramidate derivatives include the following:



Compound	R1	R2	R3	R4	Formula
300112	CH2CH2Br	Me	Me	CH2CH2Br	C ₁₇ H ₂₄ Br ₂ N ₃ O ₅ P
300113	CH2CH2Cl	CH2CH2Cl	H	H	C ₁₅ H ₂₀ Cl ₂ N ₃ O ₅ P
300114	CH2CH2Br	CH2CH2Br	H	H	C ₁₆ H ₂₀ Br ₂ N ₃ O ₅ P



300111: C17 H21 Br2 N2 O4 P

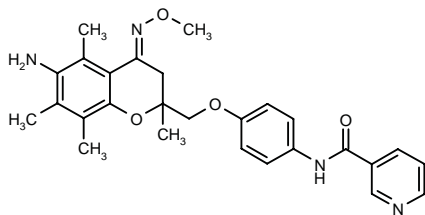
SOURCE – Purdue Research Foundation, West Lafayette, IN (US).

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1. Borch, R.F. et al. (Purdue Research Foundation) *Phosphoramidate cpds.* WO 0104130.

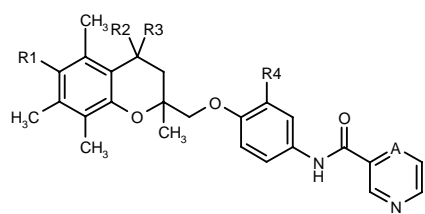
300122

N-[4-[(*E*)-6-Amino-2,5,7,8-tetramethyl-4-(methoxyimino)-3,4-dihydro-2*H*-1-benzopyran-2-ylmethoxy]phenyl]-pyridine-3-carboxamide



C27 H30 N4 O4; Mol wt: 474.5580

ACTION – Antineoplastic agent with cytotoxicity against human tumor SK-N-MC and D283-Med cell lines (IC₅₀ = 0.00163 and 0.000916 μM, respectively). Other exemplified compounds from this series of coumarone analogues include the following:



Compound	R1	R2	R3	R4	A	Formula
300124	NH2	-O-		NH2	CH	C ₂₆ H ₂₈ N ₄ O ₄
300125	NH2	-N(OMe)-		NH2	CH	C ₂₇ H ₃₁ N ₅ O ₄
300127	OAc	H	H	H	N	C ₂₇ H ₂₉ N ₃ O ₅
300128	OH	H	H	Cl	CH	C ₂₆ H ₂₇ ClN ₂ O ₄

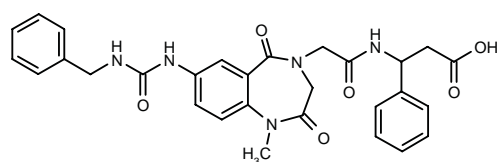
SOURCE – Sankyo.

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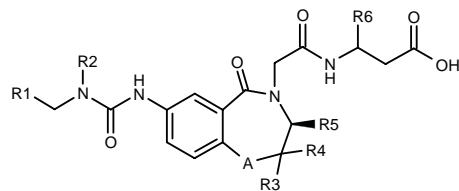
300164

3-[2-[7-(3-Benzylureido)-1-methyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-4-yl]acetamido]-3-phenylpropionic acid

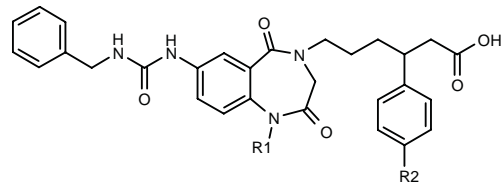


C29 H29 N5 O6; Mol wt: 543.5771

ACTION – An inhibitor of the binding of adhesive proteins such as fibrinogen, vitronectin, fibronectin, von Willebrand factor, thrombospondin and osteopontin to the vitronectin receptor (α_vβ₃) and related integrins such as α_vβ₅, α_vβ₆ and α_vβ₈ on the surface of various types of cells, thus influencing cell–cell and cell–matrix interactions. Potentially useful for the treatment or prevention of cancer, osteo-porosis, Paget’s disease, diabetic retinopathy, macular degeneration, restenosis, psoriasis, arthritis, fibrosis, renal failure and bacterial, fungal and viral infections. Other specifically claimed compounds from this series of benzazepinones and quinazolines are:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
300165	Ph	H	-O-		H	H	N(Me)	C ₂₃ H ₂₅ N ₅ O ₆
300167	Ph	H	-O-		4-OH-PhCH2	Ph	NH	C ₃₅ H ₃₃ N ₅ O ₇
300168	Ph	H	-O-		4-OH-PhCH2	Me	NH	C ₃₀ H ₃₁ N ₅ O ₇
300169	Ph	H	H	H	H	Ph	O	C ₂₈ H ₂₈ N ₄ O ₆
300170	Ph	Me	H	H	H	3-Pyr	O	C ₂₈ H ₃₀ ClN ₅ O ₆
300171	Pr	H	H	H	H	3-Pyr	O	C ₂₄ H ₂₉ N ₅ O ₆
300172	4-F-Ph	H	H	H	H	3-Pyr	O	C ₂₇ H ₂₆ FN ₅ O ₆
300173	Ph	H	H	Ph	H	Ph	O	C ₃₄ H ₃₂ N ₄ O ₆



Compound	R1	R2	Formula
300166	Me	NHCONHCH2Ph	C ₃₈ H ₄₀ N ₆ O ₆
300175	H	H	C ₂₉ H ₃₀ N ₄ O ₅

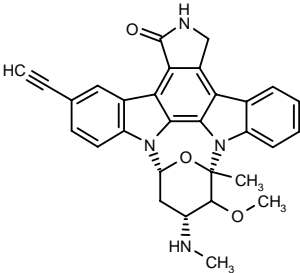
SOURCE – Roche.

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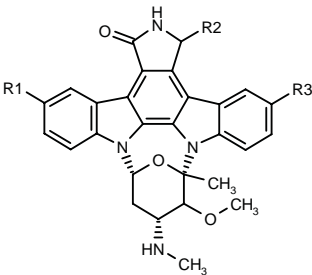
300231

(9*S*,11*R*,13*R*)-9,13-Epoxy-17-ethynyl-10-methoxy-9-methyl-11-(methylamino)-2,3,10,11,12,13-hexahydro-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*][1,7]-benzodiazonin-1-one



C30 H26 N4 O3; Mol wt: 490.5604

ACTION– Antineoplastic agent also reported to potentiate the activity of antitumor drugs, proven to inhibit the proliferation of human lung carcinoma A549 cells with an IC₅₀ value of 0.0051 μM, being more potent than UCN-01 (IC₅₀ = 0.018 μM), while exhibiting a lower binding rate to human α₁-acid glycoprotein (16.4% vs. 76.8% for UCN-01). Other exemplified compounds from this series of staurosporin derivatives include the following:



Compound	R1	R2	R3	Formula
300232	NH2	OH	NH2	C ₂₈ H ₂₈ N ₆ O ₄
300233	CHO	OH	CHO	C ₃₀ H ₂₆ N ₄ O ₆
300234	OH	OH	OH	C ₂₈ H ₂₆ N ₄ O ₆
300235	ethynylene-CH2N(Me)2	OH	H	C ₃₃ H ₃₃ N ₅ O ₄
300236	CH2OMe	H	H	C ₃₀ H ₃₀ N ₄ O ₄

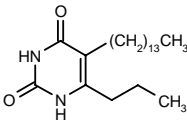
SOURCE – Kyowa Hakko.

REFERENCES

1. Kanai, F. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Staurosporin derivs*. WO 0104125.

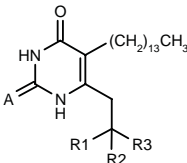
300515

6-Propyl-5-tetradecylpyrimidine-2,4(1*H*,3*H*)-dione



C21 H38 N2 O2; Mol wt: 350.5432

ACTION – Antitumor agent reported to be capable of crossing cell membranes and mimicking the effects of ceramides, inducing apoptosis of cancer cells. *In vitro*, compound exhibited cytotoxicity against human leukemia CCRF/CEM cells (IC₅₀ = 0.97 μM). Other exemplified compounds from this series of ceramide analogues include the following:



Compound	R1	R2	R3	A	Formula
300516	H	H	H	S	C ₂₀ H ₃₆ N ₂ OS
300517	H	H	H	O	C ₂₀ H ₃₆ N ₂ O ₂
300518	H	Me	Me	S	C ₂₂ H ₄₀ N ₂ OS
300519	H	Me	Me	O	C ₂₂ H ₄₀ N ₂ O ₂
300520	Me	Me	Me	S	C ₂₃ H ₄₂ N ₂ OS
300521	Me	Me	Me	O	C ₂₃ H ₄₂ N ₂ O ₂
300522	H	Ph	H	S	C ₂₆ H ₄₀ N ₂ OS
300523	H	Ph	H	O	C ₂₆ H ₄₀ N ₂ O ₂

SOURCE – Bracco.

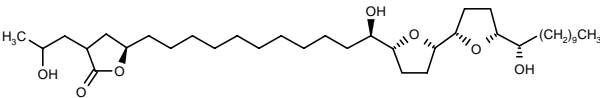
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301472

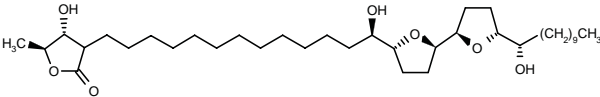
5(*R*)-[11(*R*)-Hydroxy-11-[(2*S*,2'*S*,5*R*,5*R'*)-5'-[1(*S*)-hydroxyundecyl]octahydro-2,2'-bifuran-5-yl]undecyl]-3-(2-hydroxypropyl)tetrahydrofuran-2-one

36-Dihydroisorolliniastatin 1



C37 H68 O7; Mol wt: 624.9372

ACTION – Potent inhibitor of mitochondrial complex I (IC₅₀ = 0.21 nM), a semisynthetic acetogenin (ACG) with potential antitumor activity. Another γ-lactone-function-alized ACG is:



Laherradurin [301473]: C37 H68 O7

SOURCES – Université Montpellier I, Montpellier (FR); Universidad de Valencia, Valencia (ES).

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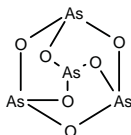
ARSENIC OXIDE

301914

2,4,6,8,9,10-Hexaoxa-1,3,5,7-tetraarsatricyclo-[3.3.1.1^{3,7}]decane

Tricyclo[3.3.1.1^{3,7}]tetraarsoxane

Tetraarsenic hexaoxide



As₄ O₆; Mol wt: 395.6820

ACTION – Arsenic compound proven to inhibit the proliferation of human cervical cancer lines including human papillomavirus (HPV)-mediated and *p53*-mutated cell lines. In these cells, compound induced arrest in the G1 phase of the cell cycle and apoptosis. In addition, compound showed antiangiogenic activity both *in vitro* and *in vivo*: in bovine capillary endothelial cells it inhibited basic fibroblast growth factor (bFGF)-induced proliferation (IC₅₀ = 99 nM) and tube formation, and *in vivo* it inhibited new vessel formation induced by bFGF in a rat corneal micropocket assay at a dose of 50 mg/kg/day p.o. for 7 days. Potentially useful for the treatment of HPV-mediated cervical cancer.

SOURCE – Catholic University of Korea, Seoul (KR).

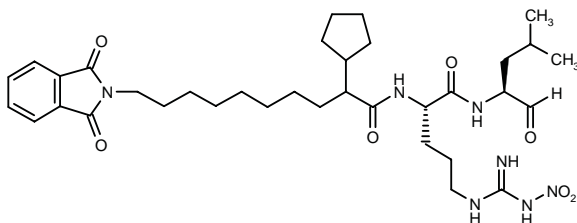
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2. Ahn, W.S. et al. *Arsenolite (As₄O₆)-mediated growth inhibition of human cervical cancer*. Proc Amer Assoc Cancer Res 2001, 42: Abst 2419.
3. Park, M.J. et al. *Arsenolite (solid As₄O₆), a novel inhibitor of angiogenesis*. Angiogenesis Cancer: Basic Mech Ther Appl. (Oct 11-15, Traverse City) 2000, Abst B25.

CEP-1612

231136

N^α-(2-Cyclopentyl-10-phthalimidodecanoyl)-*N*^ω-nitro-L-arginyl-L-leucinal



C36 H56 N6 O5; Mol wt: 652.8754

ACTION – Selective inhibitor of the chymotrypsin-like activity of the proteasome (IC₅₀ = 60 nM), reported to induce apoptosis in several human cancer cell lines including breast, prostate, brain, lung and head and neck cancer cells, but not in normal cells. In human lung cancer A549 cells, exposure to compound was associated with accumulation of the cyclin-dependent kinase (CDK) inhibitors p21^{WAF1} and p27^{KIP1}. Apoptosis was also seen in these cells, as evidenced by cleavage of PARP (poly[ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase) and activation of caspase 3. *In vivo* compound (10 mg/kg/day i.p. for 31 days) induced a significant inhibition (68%) of tumor growth in A549-bearing nude mice, which was associated with inhibition of proteasome activity in the tumor (43%), liver (80%) and kidney (50%), accumulation of the CDK inhibitors p21^{WAF1} and p27^{KIP1}, and massive apoptosis in tumors.

SOURCE – Cephalon.

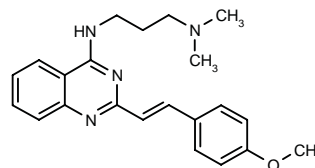
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4. Sun, J.Z. et al. *CEP1612, a dipeptidyl proteasome inhibitor, induces p21^{WAF1} and p27^{KIP1} expression and apoptosis and inhibits the growth of the human lung adenocarcinoma A-549 in nude mice*. Cancer Res 2001, 61(4): 1280.

CP-31398

302545

*N*¹-[2-[2-(4-Methoxyphenyl)vinyl]quinazolin-4-yl]-*N*³,*N*³-dimethylpropane-1,3-diamine



C22 H26 N4 O; Mol wt: 362.4744

ACTION – Antineoplastic agent able to stabilize the DNA-binding domain of mutant *p53* tumor suppressor gene. Compound induced apoptosis in 9 human cancer cell lines derived from various tissues and carrying different types of mutant *p53* or wild-type *p53*. *In vivo*, a dose of 100 mg/kg b.i.d. i.p. was able to inhibit the growth of small human tumor xenografts with naturally mutated *p53* such as melanoma A375.S2 and colon carcinoma DLD-1.

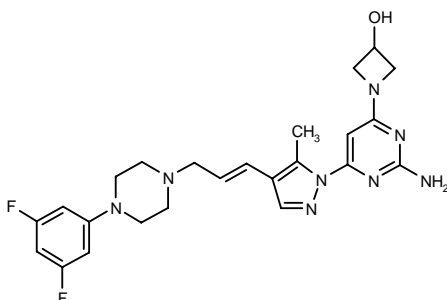
SOURCE – Pfizer.

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3. Takimoto, R. et al. *The mutant p53-conformation modifying drug, CP-31398, can induce apoptosis of human cancer cells, and can stabilize wild-type p53 protein*. Proc Amer Assoc Cancer Res 2001, 42: Abst 4952.

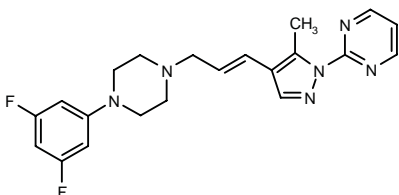
D83-7676^{*,1,3}**285989**

1-[2-Amino-6-[4-[3-[4-(3,5-difluorophenyl)piperazin-1-yl]-1(*E*)-propenyl]-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-4-yl]azetidin-3-ol



C24 H28 F2 N8 O; Mol wt: 482.5362

ACTION – Antineoplastic agent, a pyrazolypyrimidine derivative with cytotoxic activity against P-glycoprotein-producing multidrug-resistant human lung cancer PC-12 cells (GI_{50} = 3.35 ng/ml). It exhibited strong antitumor activity when given orally to nude mice bearing murine fibrosarcoma MethA or human PC-12 tumors. When compared to the parent compound **D51-1456**, this new derivative was found to induce only slight suppression of motor activity, which appeared to be related to its low brain penetration.

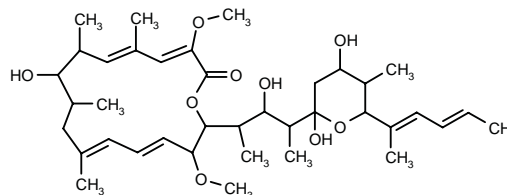
**D51-1456 [302098]^{2,3}**: C21 H22 F2 N6**SOURCE** – Daiichi Pharmaceutical.**REFERENCES**

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2. Ejima, A. et al. (Daiichi Pharmaceutical Co., Ltd.) *Pyrimidinylpyrazole deriv.* EP 0784055, JP 1997048776, US 5852019, WO 9610024.
3. Ohki, H. et al. *Synthesis and antitumor effects of pyrazolypyrimidine derivatives, novel oral anticancer agents*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)II-051.

*Identified compound **285989** Drug Data Rep 2000, 022(05): 0467.

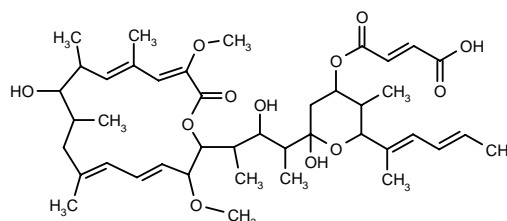
IB-97227**299822**

19,23-Epoxy-7,17,19,21-tetrahydroxy-2,14-dimethoxy-4,6,8,10,16,18,22-heptamethyloctacos-2(*Z*),4(*E*),10(*E*),12(*E*),24(*E*),26(*E*)-hexaeno-15-lactone



C38 H60 O9; Mol wt: 660.8830

ACTION – Bafilomycin derivative isolated from the culture broth of a new marine actinomycete strain ES20-008 (CECT3347), with good antitumor activity. Compound exhibited cytotoxicity *in vitro* against P388, A549, HT-29 and MEL-28 cell lines, giving IC_{50} values of 0.001, 0.001, 0.001 and 0.002 μ g/ml, respectively. In addition, it displayed antiinvasive activity in an *in vitro* assay using transwell chambers and human breast carcinoma MDA-MB-231 cells at 0.1 μ g/ml, being equipotent to bafilomycins A1, B1 and B2. Another compound isolated from the same source is:

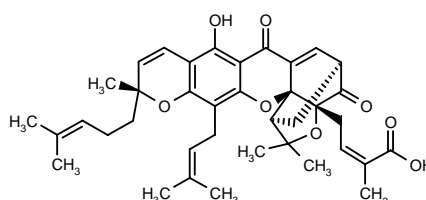
**IB-98214 [299824]**: C42 H62 O12**SOURCE** – Instituto Biomar.**REFERENCES**

1. Perez, J. et al. (Instituto Biomar SA) *Bafilomycin derivs. with anticancer activity*. WO 0102413.

MX-2060**297016**

4-[(1*R*,3*aS*,5*S*,11*R*,14*aS*)-8-Hydroxy-3,3,11-trimethyl-13-(3-methyl-2-butenyl)-11-(4-methyl-3-pentenyl)-7,15-dioxo-3*a*,4,5,7-tetrahydro-3*H*,11*H*-1,5-methanofuro[3,4-*g*]-pyrano[3,2-*b*]xanthen-1-yl]-2-methyl-2(*Z*)-butenoic acid

β -Guttiferin
Gambogic acid



C38 H44 O8; Mol wt: 628.7576

ACTION – Antineoplastic agent, a natural plant extract derived from the tree resin of *Garcinia hanburyi*, proven to induce apoptosis in cancer cells derived from human solid tumors including breast and prostate cancer. In these cells, exposure to compound was associated with rapid activation of caspase 3 and 8 ($EC_{50} = 0.5\text{--}1.5\ \mu\text{M}$), and in breast cancer T-47D cells, it induced cleavage of PARP (poly[ADP-ribose] polymerase, NAD^+ ADP-ribosyltransferase), cell shrinkage and blebbing, and nuclear fragmentation, all signs of apoptosis. In addition, growth-inhibitory activity was seen at submicromolar concentrations against most cancer cell lines tested.

SOURCE – Maxim.

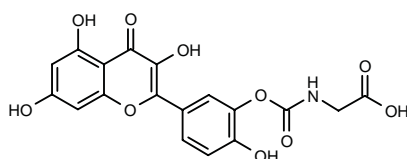
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1. Cai, S.X. et al. (Cytovia, Inc.) *Gambogic acid, analogs and derivs. as activators of caspases and inducers of apoptosis*. WO 0044216.
2. Weber, E. et al. (Cytovia, Inc.) *Methods of identifying therapeutically effective antineoplastic agents with cultured cells having intact cell membranes and corresponding products*. WO 0045165.
3. Cai, S.X. et al. *MX2060, a rapid apoptosis-inducing natural product with potent anti-tumor activity*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 226.
4. Kasibhatia, S. et al. *Apoptosis inducers as anti-cancer agents: A high-throughput screen and identification of an apoptosis-inducing natural product with a novel model of action*. Proc Amer Assoc Cancer Res 2001, 42: Abst 710.
5. *Maxim receives SBIR grant for development of caspase-inducing drugs*. DailyDrugNews.com (Daily Essentials) 2000, Nov 30.
6. *Maxim receives SBIR grants for evaluation of anticancer agents*. DailyDrugNews.com (Daily Essentials) 2001, Feb 16.

QC-12

301749

N-[2-Hydroxy-5-(3,5,7-trihydroxy-4-oxo-4*H*-1-benzopyran-2-yl)phenoxy-carbonyl]glycine



C18 H13 N O10; Mol wt: 403.2977

ACTION – Water-soluble prodrug of quercetin, a natural flavonoid anticancer agent with inhibitory activity against tyrosine kinases, but unsuitable for clinical development due to its extreme insolubility in water. A preliminary phase I study in 6 cancer patients showed the prodrug, at a dose of 400 mg (equivalent to 298 mg of quercetin) provided significant levels of quercetin following i.v. infusion but not oral administration; the relative bioavailability of quercetin in this study was 20-25% of the administered dose of prodrug. Further evaluation is warranted both as a single agent and in combination with cisplatin and paclitaxel.

SOURCE – University of Birmingham, Birmingham (GB).

REFERENCES

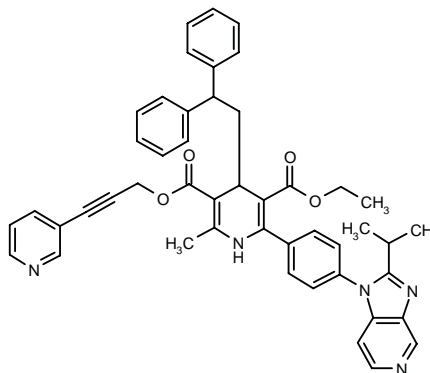
1. Golding, B.T. et al. (University of Birmingham) *Analogues or derivs. of quercetin (prodrugs)*. EP 0912541, JP 2000512988, WO 9749693.
2. Mulholland, P.J. et al. *Pharmacokinetic and bioavailability study of the quercetin prodrug, QC12*. Br J Cancer 1999, 80(Suppl. 2): 95.
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

N276-26*

282013

4-(2,2-Diphenylethyl)-2-methyl-6-[4-(2-isopropyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylic acid 5-ethyl 3-[3-(3-pyridinyl)prop-2-ynyl] diester



C47 H43 N5 O4; Mol wt: 741.8877

ACTION – Multidrug resistance modulator, a dihydropyridine derivative proven to significantly increase life span of murine leukemia P388/VCR-bearing mice when given at a dose of 3 mg/kg i.v. in combination with etoposide.

SOURCE – Nikken Chemicals.

REFERENCES

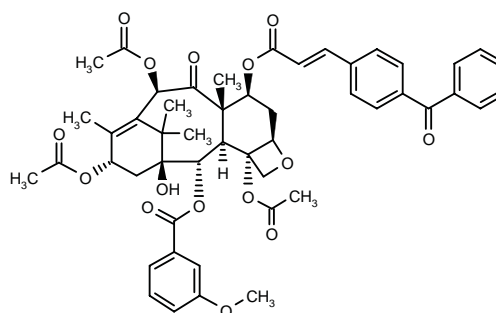
1. Tasaka, S. et al. (Nikken Chemicals Co., Ltd.) *1,4-Dihydropyridine derivs*. EP 1055672, JP 2000044559, WO 9941250.
2. Gomi, N. et al. *Synthesis of dihydropyridine derivatives with effects on multidrug resistance (4)*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-035.

*Identified compound **282013** Drug Data Rep 2000, 022(02): 0194.

SB-RA-31012011

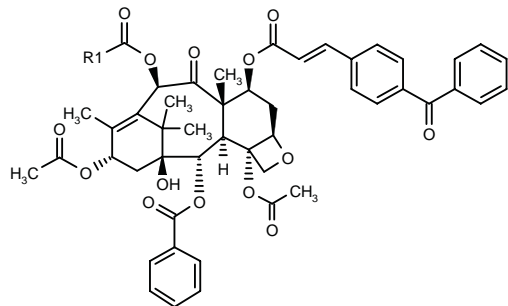
301972

3-Methoxybenzoic acid (2*aR*,4*S*,4*aS*,6*R*,9*S*,11*S*,12*S*,12*aR*,12*bS*)-6,9,12b-tris(acetoxy)-4-[3-(4-benzoylphenyl)-2(*E*)-propenyloxy]-11-hydroxy-4*a*,8,13,13-tetramethyl-5-oxo-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benzo[1,2-*b*]oxet-12-yl ester



C50 H52 O15; Mol wt: 892.9458

ACTION – Multidrug resistance modulator proven to almost completely restore the cytotoxic activity of paclitaxel in LCC6-MDR human breast cancer cells (97% reversal at 1 μ M). Other noncytotoxic taxanes include the following:



Compound	R1	Formula
SB-RA-3101220 [301970]	OMe	C ₄₉ H ₅₀ O ₁₅
SB-RA-310121 [301971]	Et	C ₅₀ H ₅₂ O ₁₄

SOURCES – Roswell Park Memorial Institute, Buffalo, NY (US); State University of New York, Stony Brook, Stony Brook, NY (US).

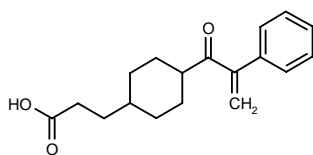
REFERENCES

1. Strum, M. et al. *Synthesis and SAR of new taxane reversal agents*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 131.

OCULAR MEDICATIONS

300053

3-[4-(2-Phenyl-2-propenoyl)cyclohexyl]propionic acid



C18 H22 O3; Mol wt: 286.3688

ACTION – Agent for the treatment of glaucoma reported to lower intraocular pressure by inducing a morphological change in trabecular cells, as demonstrated *in vitro* in cultured bovine trabecular cells (EC₅₀ = 7.7 μ M compared to 62 μ M for ethacrynic acid). A representative compound from a series of cyclohexyl fatty acid derivatives.

SOURCE – Santen.

REFERENCES

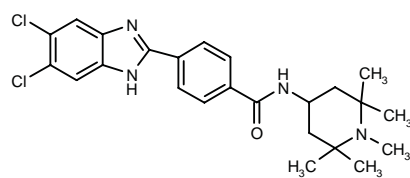
1. Shirosawa, E. et al. (Santen Pharmaceutical Co., Ltd.) *Novel cyclohexyl fatty acid derivs*. JP 2001002622.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

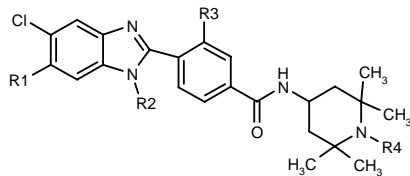
299382

4-(5,6-Dichloro-1*H*-benzimidazol-2-yl)-*N*-(1,2,2,6,6-pentamethylpiperidin-4-yl)benzamide



C24 H28 Cl2 N4 O; Mol wt: 459.4182

ACTION – Agent for the treatment of osteoporosis and related osteopenic diseases that acts by inhibiting bone resorption through selective inhibition of mammalian osteoclast vacuolar ATPase. Also reported to possess antitumor, antiviral, antiulcer, immunosuppressant, hypolipidemic, antiatherosclerotic and antiangiogenic activity. Other compounds from this series of azolyl-benzamides and analogues include the following:



Compound	R1	R2	R3	R4	Formula
299383	H	H	H	Me	C ₂₄ H ₂₉ ClN ₄ O
299384	Cl	H	OH	Me	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₂
299386	Cl	H	OMe	Me	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₂
299387	Cl	Me	OMe	Me	C ₂₆ H ₃₂ Cl ₂ N ₄ O ₂
299388	Cl	H	OEt	H	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₂

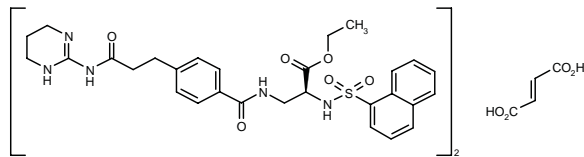
SOURCE – GlaxoSmithKline.

REFERENCES

1. Farina, C. et al. (SmithKline Beecham plc;SmithKline Beecham SpA) *Azolyl-benzamides and analogues and their use for treating osteoporosis*. WO 0100587.

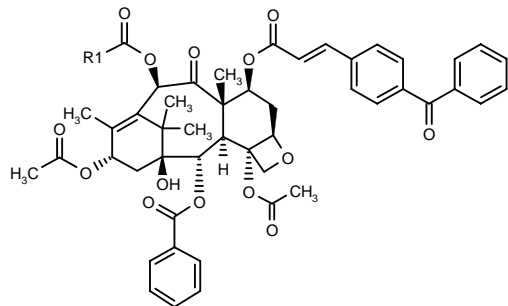
299616

2(*S*)-(1-Naphthalenylsulfonamido)-3-[4-[3-oxo-3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)propyl]benzamido]-propionic acid ethyl ester hemifumarate



2(C29 H33 N5 O6 S) . C4 H4 O4; Mol wt: 1275.4210

ACTION – Multidrug resistance modulator proven to almost completely restore the cytotoxic activity of paclitaxel in LCC6-MDR human breast cancer cells (97% reversal at 1 μ M). Other noncytotoxic taxanes include the following:



Compound	R1	Formula
SB-RA-3101220 [301970]	OMe	C ₄₉ H ₅₀ O ₁₅
SB-RA-310121 [301971]	Et	C ₅₀ H ₅₂ O ₁₄

SOURCES – Roswell Park Memorial Institute, Buffalo, NY (US); State University of New York, Stony Brook, Stony Brook, NY (US).

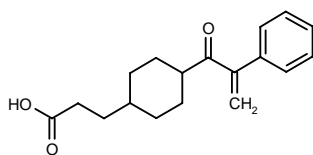
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OCULAR MEDICATIONS

300053

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SOURCE – Santen.

REFERENCES

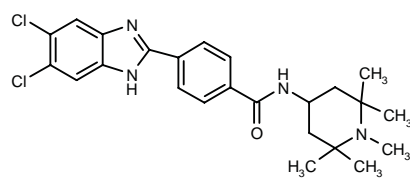
1. Shirosawa, E. et al. (Santen Pharmaceutical Co., Ltd.) *Novel cyclohexyl fatty acid derivs*. JP 2001002622.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

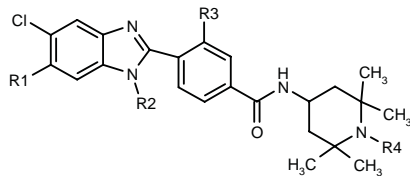
299382

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C24 H28 Cl2 N4 O; Mol wt: 459.4182

ACTION – Agent for the treatment of osteoporosis and related osteopenic diseases that acts by inhibiting bone resorption through selective inhibition of mammalian osteoclast vacuolar ATPase. Also reported to possess antitumor, antiviral, antiulcer, immunosuppressant, hypolipidemic, antiatherosclerotic and antiangiogenic activity. Other compounds from this series of azolyl-benzamides and analogues include the following:



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299386	Cl	H	OMe	Me	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₂
299387	Cl	Me	OMe	Me	C ₂₆ H ₃₂ Cl ₂ N ₄ O ₂
299388	Cl	H	OEt	H	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₂

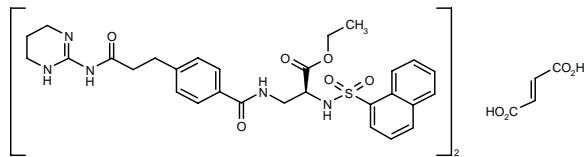
SOURCE – GlaxoSmithKline.

REFERENCES

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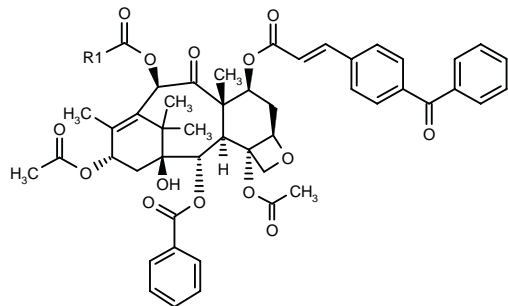
299616

2(*S*)-(1-Naphthalenylsulfonamido)-3-[4-[3-oxo-3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)propyl]benzamido]-propionic acid ethyl ester hemifumarate



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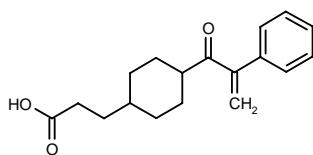
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OCULAR MEDICATIONS

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SOURCE – Santen.

REFERENCES

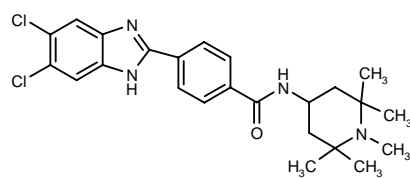
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

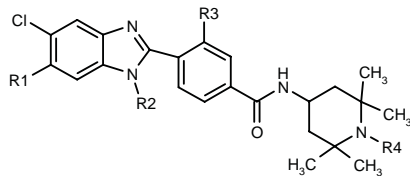
299382

4-(5,6-Dichloro-1*H*-benzimidazol-2-yl)-*N*-(1,2,2,6,6-pentamethylpiperidin-4-yl)benzamide



C24 H28 Cl2 N4 O; Mol wt: 459.4182

ACTION – Agent for the treatment of osteoporosis and related osteopenic diseases that acts by inhibiting bone resorption through selective inhibition of mammalian osteoclast vacuolar ATPase. Also reported to possess antitumor, antiviral, antiulcer, immunosuppressant, hypolipidemic, antiatherosclerotic and antiangiogenic activity. Other compounds from this series of azolyl-benzamides and analogues include the following:



Compound	R1	R2	R3	R4	Formula
299383	H	H	H	Me	C ₂₄ H ₂₉ ClN ₄ O
299384	Cl	H	OH	Me	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₂
299386	Cl	H	OMe	Me	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₂
299387	Cl	Me	OMe	Me	C ₂₆ H ₃₂ Cl ₂ N ₄ O ₂
299388	Cl	H	OEt	H	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₂

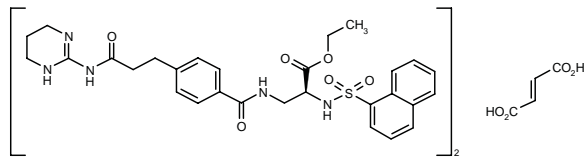
SOURCE – GlaxoSmithKline.

REFERENCES

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299616

2(*S*)-(1-Naphthalenylsulfonamido)-3-[4-[3-oxo-3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)propyl]benzamido]-propionic acid ethyl ester hemifumarate



2(C29 H33 N5 O6 S) . C4 H4 O4; Mol wt: 1275.4210

ACTION – Bone resorption inhibitor, the hemifumarate salt of a previously reported vitronectin receptor ($\alpha_v\beta_3$) antagonist with improved physicochemical properties such as nonhygroscopicity and stability compared to previously disclosed salts. When tested *in vivo* in a parathyroid hormone (PTH)-induced hypercalcemia model in thyroparathyroidectomized rats, compound produced a 45% decrease in serum calcium concentrations when administered at 10 mg/kg p.o. at 0 and 3 h after the start of the PTH infusion.

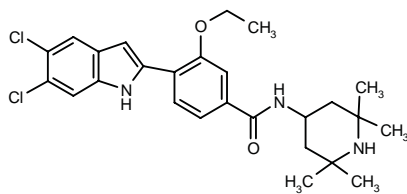
SOURCE – Aventis Pharma.

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1. Breipohl, G. et al. (Aventis Pharma Deutschland GmbH) 1,4,5,6-Tetrahydropyrimidine deriv. as a vitronectin inhibitor. EP 1070707, WO 0107417.

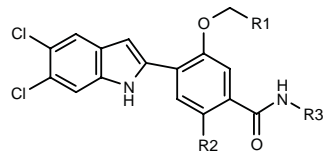
299691

4-(5,6-Dichloro-1*H*-indol-2-yl)-3-ethoxy-*N*-(2,2,6,6-tetramethylpiperidin-4-yl)benzamide



C26 H31 Cl2 N3 O2; Mol wt: 488.4559

ACTION – Agent for the treatment or prevention of diseases associated with overactivity of osteoclasts such as osteoporosis that acts by inhibiting bone resorption through selective inhibition of mammalian osteoclast vacuolar ATPase. Also reported to possess antitumor, antiviral, antiulcer, immunosuppressant, hypolipidemic, antiatherosclerotic and antiangiogenic activity, and to be useful for the treatment of AIDS and Alzheimer's disease. Other specifically claimed compounds from this series of indole derivatives include the following:



Compound	R1	R2	R3	Formula
299692	H	H	4-(3-MeO-Ph)-1-Piz-(CH2)3	C ₃₀ H ₃₂ Cl ₂ N ₄ O ₃
299693	Me	H	1,2,2,6,6-(Me)5-4-Pip	C ₂₇ H ₃₃ Cl ₂ N ₃ O ₂
299695	H	OMe	2,2,6,6-(Me)4-4-Pip	C ₂₆ H ₃₁ Cl ₂ N ₃ O ₃
299696	H	H	1-[EtOCO(CH2)5]-4-Pip	C ₂₉ H ₃₅ Cl ₂ N ₃ O ₄
299697	H	H	1-[CO2H(CH2)4]-4-Pip	C ₂₆ H ₂₉ Cl ₂ N ₃ O ₄
299698	(S)-CH(OH)-CH2OH	H	2,2,6,6-(Me)4-4-Pip	C ₂₇ H ₃₃ Cl ₂ N ₃ O ₄

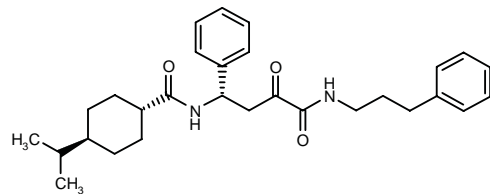
SOURCE – GlaxoSmithKline.

REFERENCES

1. Farina, C. et al. (SmithKline Beecham SpA) Indole derivs. and their use for the treatment of osteoporosis amongst other applications. WO 0102388.

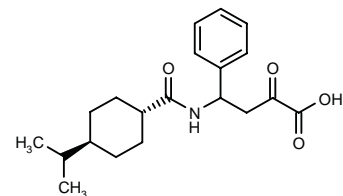
300559

trans-4-Isopropyl-*N*-[3,4-dioxo-1(*S*)-phenyl-4-(3-phenylpropylamino)butyl]cyclohexanecarboxamide



C29 H38 N2 O3; Mol wt: 462.6302

ACTION – An inhibitor of cysteine proteases such as cathepsin L and cathepsin S (IC₅₀ = 24 and 72 nM, respectively), with potential in the treatment of osteoporosis, rheumatoid arthritis, Alzheimer's disease, Behçet's disease, asthma, thrombosis, cerebral ischemia, apoptosis, cancer metastasis, cataracts and neuronal death. Another compound from this series of cycloalkane carboxylic acid amide derivatives is:



300560: C20 H27 N O4

SOURCE – Kissei.

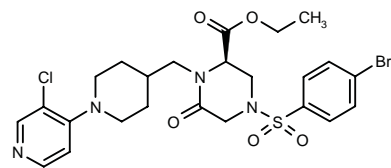
REFERENCES

1. Sato, M. et al. (Kissei Pharmaceutical Co., Ltd.) Cycloalkane carboxylic acid amide derivs. JP 2001011037.

TREATMENT OF LIPOPROTEIN DISORDERS

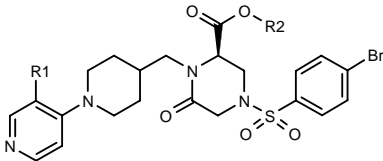
299352

4-(4-Bromophenylsulfonyl)-1-[1-(3-chloropyridin-4-yl)piperidin-4-ylmethyl]-6-oxopiperazine-2(*R*)-carboxylic acid ethyl ester



C24 H28 Br Cl N4 O5 S; Mol wt: 599.9312

ACTION – An inhibitor of cholesterol biosynthesis (69% inhibition in cultured murine fibroblast L929 cells at 0.01 µg/ml) that is reported to act by inhibiting 2,3-oxidosqualene cyclase. Other exemplified compounds from this series of aromatic compounds bearing cyclic amino groups include the following:



Compound	R1	R2	Formula
299353	H	Et	C ₂₄ H ₂₉ BrN ₄ O ₅ S
299354	H	H	C ₂₂ H ₂₅ BrN ₄ O ₅ S
299355	Cl	H	C ₂₂ H ₂₄ BrClN ₄ O ₅ S

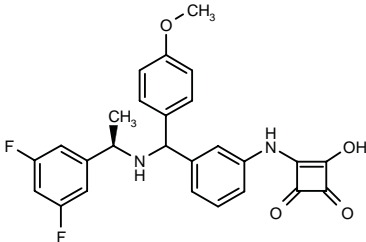
SOURCE – Mochida.

REFERENCES

1. Nishida, H. and Hosaka, Y. (Mochida Pharmaceutical Co., Ltd.) *Cholesterol biosynthesis inhibitors containing as the active ingredient aromatic cpds. bearing cyclic amino groups.* WO 0100616.

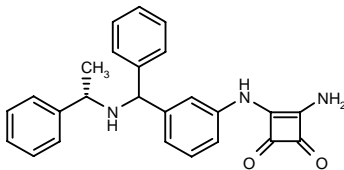
299624

3-[3-[1-[1(*R*)-(3,5-Difluorophenyl)ethylamino]-1-(4-methoxyphenyl)methyl]phenylamino]-4-hydroxy-3-cyclobutene-1,2-dione



C26 H22 F2 N2 O4; Mol wt: 464.4658

ACTION – Agent for the treatment or prevention of hypercholesterolemia with excellent ileal bile acid transporter-inhibitory activity, as demonstrated *in vivo* in hamsters by 80.0% inhibition of [³H]-taurocholic acid uptake into the gallbladder bile at 100 mg/kg p.o. Another compound from this series of cyclobutene derivatives is:



299625: C25 H23 N3 O2

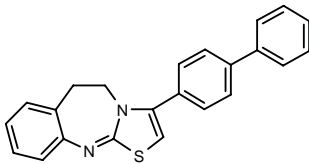
SOURCE – Sankyo.

REFERENCES

1. Hitoshi, K. et al. (Sankyo Co., Ltd.) *Cyclobutene derivs.* EP 1070703, JP 2001089429.

299673

3-(Biphenyl-4-yl)-5,6-dihydrothiazolo[2,3-*b*][1,3]benzodiazepine



C23 H18 N2 S; Mol wt: 354.4752

ACTION – Agent for the treatment of dyslipidemia, atherosclerosis, diabetes and complications of diabetes that acts by decreasing the secretion of apolipoprotein CIII (apo CIII), as demonstrated in cultured human HepG2 hepatocytes (IC₅₀ = 17.4 µM).

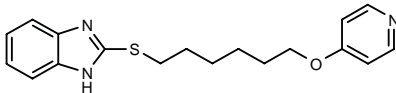
SOURCE – Merck & Co.

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1. Berthelon, J.-J. et al. (Merck Patent GmbH) *Dihydrobenzodiazepins and their use for treating dyslipidemia.* FR 2796070, WO 0102373.

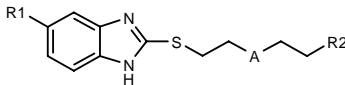
300242

2-[6-(4-Pyridinyloxy)hexylsulfanyl]-1-*H*-benzimidazole



C18 H21 N3 O S; Mol wt: 327.4499

ACTION – Hypolipidemic and antiatherosclerotic agent with macrophage foaming and ACAT-inhibitory activity. Compound was shown to potently inhibit the formation of cholesterol esters in murine peritoneal macrophages at 5 µM. In addition, it inhibited ACAT from thoracic aorta microsomes of cholesterol-fed rabbits with an IC₅₀ value of 7.9 µM. Other exemplified compounds within this series of benzimidazole derivatives include the following:



Compound	R1	R2	A	Formula
300243	H	1-Me-2-benzimidazolyl-O	CH2	C ₂₀ H ₂₂ N ₄ OS
300244	H	4-Pyr-O	CH2	C ₁₇ H ₁₉ N ₃ OS
300245	H	2-benzothiazolyl-NH	CH2	C ₁₉ H ₂₀ N ₄ S ₂
300246	H	2-benzoxazolyl-NH	CH2	C ₁₉ H ₂₀ N ₄ OS
300247	Me	2-benzoxazolyl-NH	CH2	C ₂₀ H ₂₂ N ₄ OS
300248	H	2-benzoxazolyl-NH	O	C ₁₈ H ₁₈ N ₄ O ₂ S

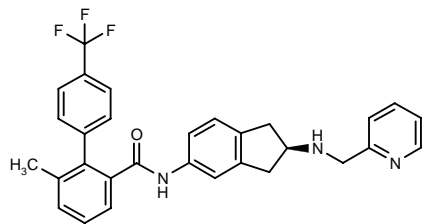
SOURCE – Fuji Photo Film.

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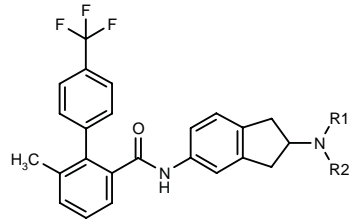
300282

6-Methyl-*N*-[2(*R*)-(2-pyridinylmethylamino)indan-5-yl]-4'-(trifluoromethyl)biphenyl-2-carboxamide

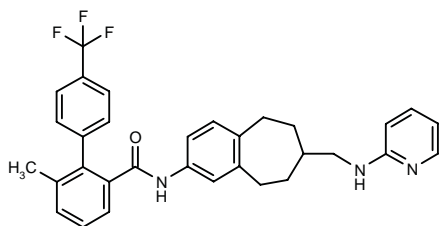


C30 H26 F3 N3 O; Mol wt: 501.5494

ACTION – An inhibitor of microsomal triglyceride transfer protein (MTP) and of apolipoprotein B (ApoB) secretion, which gave about 86% inhibition at 0.1 μM in an ApoB assay and an IC₅₀ value of about 120 nM in an MTP assay. *In vivo*, compound is reported to lower both plasma triglyceride and cholesterol levels at a dose of 5 mg/kg p.o. Potentially useful for the treatment and prevention of conditions related to elevated levels of MTP and ApoB such as hyperlipidemia, hypercholesterolemia and hypertriglyceridemia, and diseases associated therewith such as cardiovascular diseases including cardiac ischemia, atherosclerosis, obesity, pancreatitis and diabetes. Other specifically claimed compounds from this series of heteroar(alkyl)amino-benzocycloalkane substituted amide derivatives are:



Compound	R1	R2	Formula
300283	2-imidazolyl-CH2	H	C ₂₈ H ₂₅ F ₃ N ₄ O
300285	3-thienyl-CH2	3-thienyl-CH2	C ₃₄ H ₂₉ F ₃ N ₂ OS ₂
300286	2-Pyr-CH2	Me	C ₃₁ H ₂₈ F ₃ N ₃ O
300287	2-Pyr	H	C ₂₉ H ₂₄ F ₃ N ₃ O



300284: C32 H30 F3 N3 O

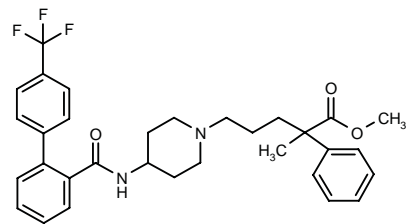
SOURCE – Novartis.

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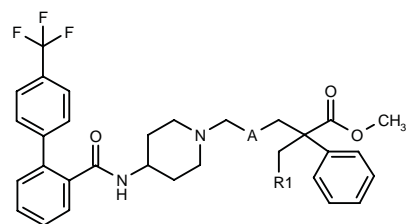
300301

2-Methyl-2-phenyl-5-[4-[4'-(trifluoromethyl)biphenyl-2-yl]carboxamido]piperidin-1-yl]pentanoic acid methyl ester



C32 H35 F3 N2 O3; Mol wt: 552.6335

ACTION – Agent for the treatment of hyperlipidemia, atherosclerosis, diabetes mellitus, obesity and pancreatitis, an inhibitor of microsomal triglyceride transfer protein (MTP). Other specifically claimed compounds from this series of biphenyl derivatives are:



Compound	R1	A	Formula
300305	Me	-CH2-	C ₃₃ H ₃₇ F ₃ N ₂ O ₃
300308	H	-(CH2)2-	C ₃₃ H ₃₇ F ₃ N ₂ O ₃

SOURCE – Boehringer Ingelheim.

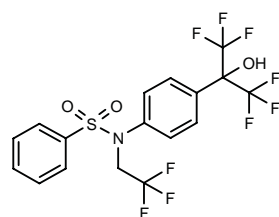
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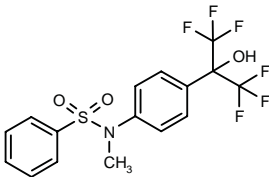
301638

N-(2,2,2-Trifluoroethyl)-*N*-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]benzenesulfonamide



C17 H12 F9 N O3 S; Mol wt: 481.3338

ACTION – Liver X receptor (LXR) agonist with potential for increasing HDL cholesterol levels and thus for the treatment of disorders associated with cholesterol metabolism and fatty acid biosynthesis including gallstones, coronary heart disease and atherosclerosis. Another related compound is:



T-0314407 [301639]: C16 H13 F6 N O3 S

SOURCE – Tularik.

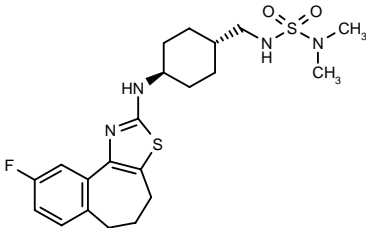
REFERENCES

1. Shan, B. (Tularik Inc.) *Compsns. and methods for raising HDL cholesterol levels*. WO 0103705.
2. Medina, J.C. et al. *Discovery and optimization of activators of the nuclear receptor LXRα*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 180.

TREATMENT OF OBESITY
AND NUTRITIONAL DISORDERS

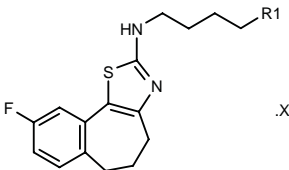
300045

trans-*N*'-[4-(9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]-cyclohepta[1,2-*d*]thiazol-2-ylamino)cyclohexylmethyl]-*N,N*-dimethylsulfamide

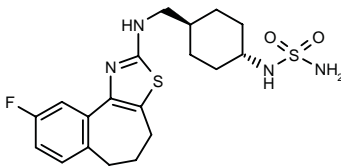


C21 H29 F N4 O2 S2; Mol wt: 452.6161

ACTION – Potent and selective human neuropeptide Y (NPY) Y₅ receptor antagonist, as demonstrated in binding assays by a K_i value of 2.1 nM against cloned human Y₅ receptors, compared to K_i values > 10,000 nM against cloned human Y₁, Y₂ and Y₄ receptor subtypes. Potentially useful for the treatment of eating disorders such as obesity and bulimia, sexual and reproductive disorders, depression, epilepsy, hypertension, cerebral hemorrhage, congestive heart failure and sleep disorders. Other exemplified bicyclic and tricyclic compounds include the following:



Compound	R ₁	X	Formula
300046	CH ₂ NHSO ₂ Me	HCl	C ₁₈ H ₂₄ FN ₃ O ₂ S ₂ ·HCl
300047	CH ₂ NHSO ₂ N(Et) ₂	HCl	C ₂₁ H ₃₁ FN ₄ O ₂ S ₂ ·HCl
300048	CH ₂ NHSO ₂ Et		C ₁₉ H ₂₆ FN ₃ O ₂ S ₂
300049	NHSO ₂ N(Et) ₂		C ₂₀ H ₂₉ FN ₄ O ₂ S ₂
300050	CH ₂ NHSO ₂ NH ₂		C ₁₇ H ₂₃ FN ₄ O ₂ S ₂



300051:C19 H25 F N4 O2 S2

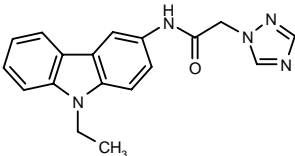
SOURCES – Novartis; Synaptic.

REFERENCES

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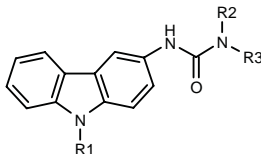
300489

N-(9-Ethyl-9*H*-carbazol-3-yl)-2-(1*H*-1,2,4-triazol-1-yl)-acetamide



C18 H17 N5 O; Mol wt: 319.3663

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist, expected to be useful for the treatment of eating disorders such as obesity. Other exemplified carbazole derivatives include the following



Compound	R1	R2	R3	Formula
300490	Et	-CH ₂ CH ₂ OCH ₂ CH ₂ -		C ₁₉ H ₂₁ N ₃ O ₂
300491	Et	Me	1-Me-4-Pip	C ₂₂ H ₂₈ N ₄ O
300492	SO ₂ Me	-CH ₂ CH ₂ OCH ₂ CH ₂ -		C ₁₈ H ₁₉ N ₃ O ₄ S

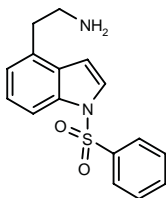
SOURCE – AstraZeneca.

REFERENCES

1. Block, M.H. et al. (AstraZeneca plc) *Carbazole derivs. and their use as neuropeptide Y5 receptor ligands*. WO 0107409.

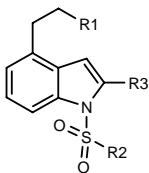
300544

2-[1-(Phenylsulfonyl)-1*H*-indol-4-yl]ethylamine



C16 H16 N2 O2 S; Mol wt: 300.3804

ACTION – Selective 5-HT₆ receptor ligand, potentially useful in the treatment of 5-HT₆-mediated disorders such as anorexia, bulimia, cocaine, alcohol, nicotine or benzo-diazepine addiction, and irritable bowel syndrome. Other specifically claimed compounds from this series of indole and indoline derivatives are:



Compound	R1	R2	R3	Formula
300545	N(Me)2	Ph	H	C ₁₈ H ₂₀ N ₂ O ₂ S
300546	N(Me)2	N(Me)2	H	C ₁₄ H ₂₁ N ₃ O ₂ S
300547	CH ₂ N(Me)2	Ph	H	C ₁₉ H ₂₂ N ₂ O ₂ S
300548	N(Me)2	Ph	COPh	C ₂₅ H ₂₄ N ₂ O ₃ S

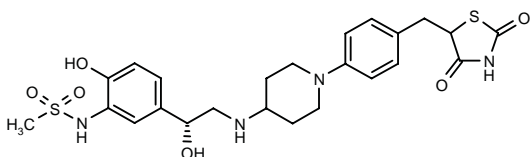
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Mc Allister, G. et al. (Merck Sharp & Dohme Ltd.) *Indole and indoline derivs. as 5-HT₆ selective ligands*. US 6187805.

302635

N-[5-[2-[1-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenyl]-piperidin-4-ylamino]-1(*R*)-hydroxyethyl]-2-hydroxyphenyl]-methanesulfonamide



C₂₄ H₃₀ N₄ O₆ S₂; Mol wt: 534.6550

ACTION – Potent and selective β₃-adrenoceptor agonist (EC₅₀ = 10 nM for stimulation of cAMP accumulation in CHO cells expressing human β₃-adrenoceptors) with more than 110-fold selectivity over both β₁- and β₂-adrenoceptors. Compound induced thermogenesis in human β₃-adrenoceptor transgenic mice (30% thermogenesis at 10 mg/kg i.p.) but not in β₃-adrenoceptor knockout mice. Potentially useful for the treatment of obesity and type 2 diabetes.

SOURCE – Wyeth-Ayerst.

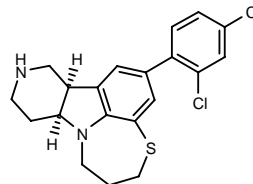
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IK-264

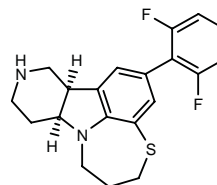
301822

(8*aS*,12*aR*)-2-(2,4-Dichlorophenyl)-6,7,8*a*,9,10,11,12,12*a*-octahydro-5*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*ef*]-[1,5]benzothiazepine



C₂₀ H₂₀ Cl₂ N₂ S; Mol wt: 391.3640

ACTION – Potent and selective 5-HT_{2C} receptor ligand with respective K_i values of 10.5 and 406 nM for binding affinity at 5-HT_{2C} and 5-HT_{2A} receptors. In functional experiments compound showed partial agonist activity at 5-HT_{2C} receptors, with an EC₅₀ value of 250 nM. Compound was orally available and effective in chronic feeding studies in rats where it strongly reduced body weight at doses 1-3 mg/kg. Potentially useful for the treatment of obesity. Another related compound is:



IL-639 [301823]: C₂₀ H₂₀ F₂ N₂ S

SOURCE – DuPont Pharmaceuticals.

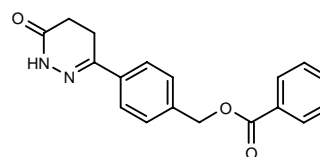
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2. Robichaud, A.J. et al. *Synthesis and biological evaluation of novel, selective 5-HT_{2C} receptor agonists for the treatment of obesity*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 105.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

299423

Benzoic acid 4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-benzyl ester



C₁₈ H₁₆ N₂ O₃; Mol wt: 308.3354

ACTION – A representative compound from a series of dihydropyridazinones reported to increase human erythrocyte precursor cell proliferation *in vitro* and hematocrit in mice. Potentially useful for the treatment of anemia.

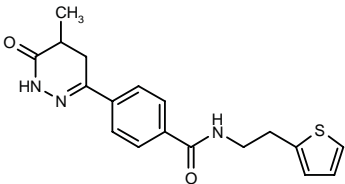
SOURCE – Bayer.

REFERENCES

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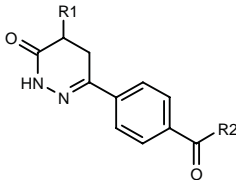
299425

4-(5-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-N-[2-(2-thienyl)ethyl]benzamide



C18 H19 N3 O2 S; Mol wt: 341.4331

ACTION – Agent for the treatment of anemia that is reported to increase human erythrocyte precursor cell proliferation *in vitro* and hematocrit in mice. Other exemplified 6-carboxyphenylpyridazinones are:



Compound	R1	R2	Formula
299427	Me	cyclopentyl-O	C ₁₇ H ₂₀ N ₂ O ₃
299429	H	2-F-PhNH	C ₁₇ H ₁₄ FN ₃ O ₂

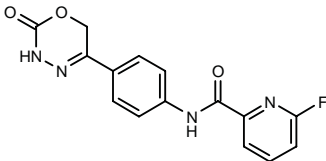
SOURCE – Bayer.

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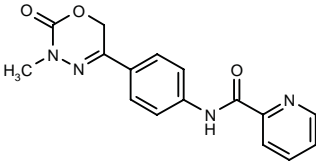
299430

6-Fluoro-N-[4-(2-oxo-3,6-dihydro-2H-1,3,4-oxadiazin-5-yl)phenyl]pyridine-2-carboxamide



C15 H11 F N4 O3; Mol wt: 314.2749

ACTION – Agent for the treatment of anemia that is reported to increase human erythrocyte precursor cell proliferation *in vitro* and hematocrit in mice. Other exemplified 2-oxodihydrooxadiazines are:



299431: C16 H14 N4 O3

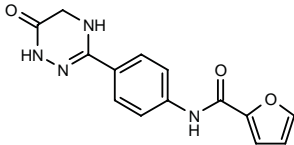
SOURCE – Bayer.

REFERENCES

1. Stolfuss, J. et al. (Bayer AG) *Novel 4-(2-oxodihydrooxadiazinyl)phenyl)amides and their use thereof for treating anemia*. DE 19929787, WO 0100601.

299432

N-[4-(6-Oxo-1,4,5,6-tetrahydro-1,2,4-triazin-3-yl)phenyl]-furan-2-carboxamide



C14 H12 N4 O3; Mol wt: 284.2738

ACTION – A representative compound from a series of 6-oxotetrahydrotriazines reported to increase human erythrocyte precursor cell proliferation *in vitro* and hematocrit in mice. Potentially useful for the treatment of anemia.

SOURCE – Bayer.

REFERENCES

1. Stolfuss, J. et al. (Bayer AG) *N-[4-(6-Oxotetrahydrotriazinyl)phenyl]amides and use thereof*. DE 19929781, WO 0100598.

PEGNARTOGRASTIM

Prop INN; USAN

253186

N-L-Methionyl-1-L-alanine-3-L-threonine-4-L-tyrosine-5-L-arginine-17-L-serine-colony-stimulating factor (human clone 1034), reaction product with succinic anhydride, esters with polyethylene glycol mono-methyl ether

PEG-ND-28
Ro-25-8315
Ro-25-8315/000

ACTION – Pegylated derivative of the recombinant human granulocyte colony-stimulating factor (rhG-CSF) mutant KW-2228 (nartograstim*), reported to stimulate the proliferation and differentiation of neutrophil precursors, leading to an increase in the number of circulating neutrophils. A phase I study in healthy volunteers in which compound was administered as a single dose (10-150 µg/kg) and compared with rhG-CSF (filgrastim; 5-10 µg/kg) showed an improved pharmacokinetic profile compared to rhG-CSF, with a longer elimination half-life and a much longer duration of action. A comparable effect to rhG-CSF was seen on increase in absolute neutrophil

count and peripheral blood mononuclear cell mobilization. In breast cancer patients undergoing chemotherapy, compound at dose of 100 µg/kg induced optimal mobilization of peripheral blood progenitor cells in non-neutropenic patients. Potentially useful for the treatment of myelosuppression associated with chemotherapy.

SOURCES – Kyowa Hakko; Roche.

REFERENCES

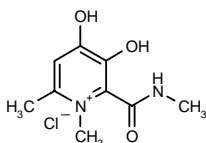
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*Drug Data Rep 1994, 016(11): 1012.

TREATMENT OF POISONING , DRUG ABUSE AND DEPENDENCY

302808

3,4-Dihydroxy-1,6-dimethyl-2-(*N*-methylcarbamoyl)-pyridinium chloride



C9 H13 N2 O3 . Cl; Mol wt: 232.6657

ACTION – Oral iron chelator with a pFe^{3+} value of 21.7, more than 2 orders of magnitude higher than that of deferiprone ($pFe^{3+} = 19.4$). In rats compound showed good oral absorption, with reduced penetration into the blood–brain barrier and low toxicity. In [^{59}Fe]-ferritin-loaded rats, compound at 150 µmol/kg showed iron-scavenging activity superior to that of deferiprone at 450 µmol/kg. Potentially useful for the treatment of complications associated with elevated iron levels during blood transfusion.

SOURCE – King's College London, London (GB).

REFERENCES

1. Liu, Z.D. et al. *Synthesis of 2-amino-3-hydroxypyridin-4(1H)-ones: Novel iron chelators with enhanced pFe^{3+} values*. Bioorg Med Chem 2001, 9(3): 563.

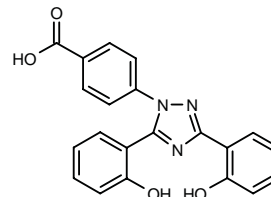
ICL-670

280627

4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid

CGP-72670

ICL-670A



C21 H15 N3 O4; Mol wt: 373.3665

ACTION – Synthetic oral iron chelator able to promote the excretion of chelatable iron from hepatocellular and reticuloendothelial iron stores when given orally to hypertransfused rats. In this model, the effect of compound was greater than that of deferoxamine (DFO), and when the two chelators were given in combination their effects were additive at lower doses. Compound was found to be less effective than DFO in removing iron from iron-loaded heart cells but coadministration of the two compounds resulted in improved chelating efficiency for ICL-670, which appeared to be attributable to an exchange of iron between DFO and ICL-670. A phase I single-dose safety study in adult male patients with transfusion-dependent β -thalassemia showed compound (2.5, 5, 10, 20, 40 and 80 mg/kg) to be generally well tolerated, with only mild and transient side effects. The median t_{max} was consistently in the range of 2-3 h at the doses tested, while mean C_{max} and $AUC_{(0-24h)}$ values increased by 30-fold from the lowest to the highest dose. Compound is undergoing further clinical evaluation for the treatment of iron-overloaded patients.

SOURCE – Novartis.

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6. Hershko, C. et al. *ICL670A: A new synthetic oral chelator: Evaluation in hypertransfused rats with selective radioiron probes of hepatocellular and reticuloendothelial iron stores and in iron-loaded rat heart cells in culture*. Blood 2001, 97(4): 1115.
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8. Piga, A. et al. *A novel oral iron chelator (ICL670A): Results of a phase I single-dose safety study*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 3304.

count and peripheral blood mononuclear cell mobilization. In breast cancer patients undergoing chemotherapy, compound at dose of 100 µg/kg induced optimal mobilization of peripheral blood progenitor cells in non-neutropenic patients. Potentially useful for the treatment of myelosuppression associated with chemotherapy.

SOURCES – Kyowa Hakko; Roche.

REFERENCES

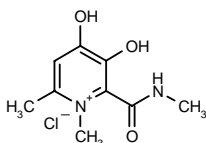
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*Drug Data Rep 1994, 016(11): 1012.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

302808

3,4-Dihydroxy-1,6-dimethyl-2-(*N*-methylcarbamoyl)-pyridinium chloride



C9 H13 N2 O3 . Cl; Mol wt: 232.6657

ACTION – Oral iron chelator with a pFe^{3+} value of 21.7, more than 2 orders of magnitude higher than that of deferiprone ($pFe^{3+} = 19.4$). In rats compound showed good oral absorption, with reduced penetration into the blood–brain barrier and low toxicity. In $[^{59}Fe]$ -ferritin-loaded rats, compound at 150 µmol/kg showed iron-scavenging activity superior to that of deferiprone at 450 µmol/kg. Potentially useful for the treatment of complications associated with elevated iron levels during blood transfusion.

SOURCE – King's College London, London (GB).

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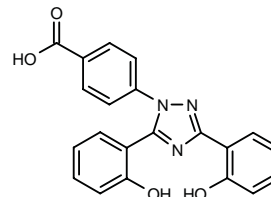
ICL-670

280627

4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid

CGP-72670

ICL-670A



C21 H15 N3 O4; Mol wt: 373.3665

ACTION – Synthetic oral iron chelator able to promote the excretion of chelatable iron from hepatocellular and reticuloendothelial iron stores when given orally to hypertransfused rats. In this model, the effect of compound was greater than that of deferoxamine (DFO), and when the two chelators were given in combination their effects were additive at lower doses. Compound was found to be less effective than DFO in removing iron from iron-loaded heart cells but coadministration of the two compounds resulted in improved chelating efficiency for ICL-670, which appeared to be attributable to an exchange of iron between DFO and ICL-670. A phase I single-dose safety study in adult male patients with transfusion-dependent β -thalassemia showed compound (2.5, 5, 10, 20, 40 and 80 mg/kg) to be generally well tolerated, with only mild and transient side effects. The median t_{max} was consistently in the range of 2-3 h at the doses tested, while mean C_{max} and $AUC_{(0-24h)}$ values increased by 30-fold from the lowest to the highest dose. Compound is undergoing further clinical evaluation for the treatment of iron-overloaded patients.

SOURCE – Novartis.

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6. Hershko, C. et al. *ICL670A: A new synthetic oral chelator: Evaluation in hypertransfused rats with selective radioiron probes of hepatocellular and reticuloendothelial iron stores and in iron-loaded rat heart cells in culture*. Blood 2001, 97(4): 1115.
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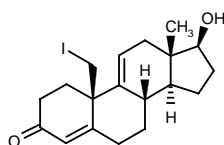
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DIAGNOSTIC AGENTS

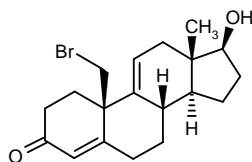
300298

17 β -Hydroxy-19-iodoandrosta-4,9(11)-dien-3-one



C19 H25 I O2; Mol wt: 412.3045

ACTION – A representative compound from a series of 17 β -hydroxy-19-halogen-androsta-4,9(11)-diene-3-one derivatives with high affinity for androgen receptors; the corresponding radiolabeled compounds are reported to be useful for prostate imaging and for the diagnosis of prostatic disorders. Compound is also useful for the preparation of further steroid derivatives with anti-androgen activity for the treatment of androgen-dependent disorders such as prostatic carcinoma and prostatic hyperplasia. Another exemplified compound from this series of C19-halogen-substituted steroids derivatives is:



300299: C19 H25 Br O2

SOURCE – Schering AG.

REFERENCES

1. Neef, G. et al. (Schering AG) *Novel C-19-halogen-subst. steroids of the androst-9(11)-ene-series, methods for the production and use thereof.* DE 19934088, WO 0105805.

NT-proBNP

300792

N-Terminal pro brain natriuretic peptide

ACTION – N-terminal pro brain natriuretic peptide, a potential marker for heart failure. Plasma levels of NT-proBNP appear to be dependent on age and gender, according to a study in 683 unselected subjects with a mean age of 68 years. Normal subjects showed a marked increase in NT-proBNP levels with increasing age. Moreover, women had significantly higher NT-proBNP levels than men across all age groups. Several clinical studies in myocardial infarction patients demonstrated the utility of the NT-proBNP as a marker for left ventricular systolic dysfunction, as well as for the clinical diagnosis of heart failure.

SOURCE – Roche Diagnostics.

REFERENCES

- Ng, L.K. *Natriuretic peptide fragments.* WO 0035951.
- Campbell, D.J. et al. *Plasma amino-terminal pro-brain natriuretic peptide: A novel approach to the diagnosis of cardiac dysfunction.* J Cardiac Fail 2000, 6(2): 130.
- Clerico, A. et al. *Clinical relevance of cardiac natriuretic peptides measured by means of competitive and non-competitive immunoassay methods in patients with renal failure on chronic hemodialysis.* J Endocrinol Invest 2001, 24(1): 24.
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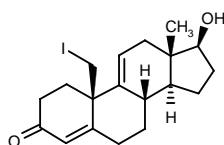
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DIAGNOSTIC AGENTS

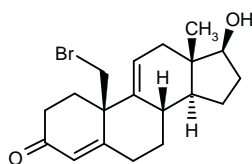
300298

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C19 H25 I O2; Mol wt: 412.3045

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SOURCE – Roche Diagnostics.

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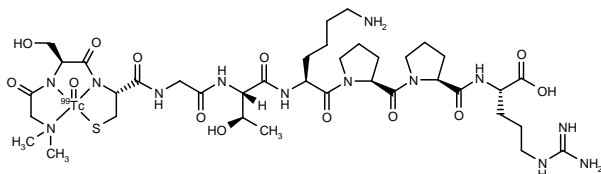
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Tc-99m-RP-128

217951

(*SP-5-25*)-Hydrogen [*N,N*-dimethylglycyl- κ *N*-L-seryl- κ *N*-L-cysteinyl- κ *N*, κ *S*-glycyl-L-threonyl-L-lysyl-L-prolyl-L-prolyl-L-argininato(4-)]oxotechnetate(1-)-^{99m}Tc

^{99m}Tc-RP-128



C38 H64 N13 O13 S Tc; Mol wt: 1042.0680

ACTION – Bifunctional peptide chelate radiopharmaceutical that binds *in vivo* to the tuftsin receptor located specifically on neutrophils and monocyte-macrophages, suitable for imaging of acute and chronic inflammation including Crohn's disease, rheumatoid arthritis and CNS inflammation such as multiple sclerosis. The radiopharmaceutical showed favorable biodistribution characteristics in humans, with no significant accumulation in major organs.

SOURCES – CIS Bio International (Schering AG); Resolution Pharmaceuticals.

REFERENCES

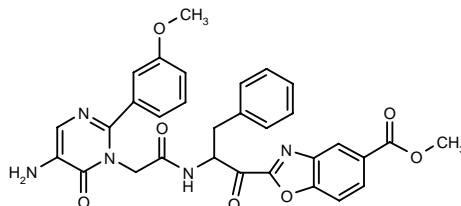
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11. Allelix Biopharmaceuticals Inc. First Quarter Report 1996.

PHARMACOLOGICAL TOOLS

Y-40079*

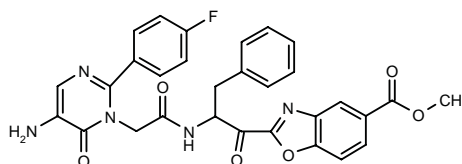
266115

2-[2-[2-[5-Amino-2-(3-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-1-yl]acetamido]-3-phenylpropionyl]benzoxazole-5-carboxylic acid methyl ester



C31 H27 N5 O7; Mol wt: 581.5823

ACTION – Potent human chymase inhibitor ($IC_{50} = 4.85$ nM) that is also active against several animal chymases but selective relative to other proteases including chymotrypsin and cathepsin G ($IC_{50} = 943$ and 379 nM, respectively), as well as leukocyte elastase, thrombin and angiotensin-converting enzyme ($IC_{50} > 10$ μ M). Good oral bioavailability was observed in rats (19.3%), where it was slowly absorbed ($t_{max} = 6.0$ h after 1 mg/kg p.o.) and eliminated ($t_{1/2} = 35.7$ h after 1 mg/kg i.v.). Potentially useful as a tool for elucidating the physiological and pathophysiological role of chymase. Another related compound is:



Y-40613 [302793]: C30 H24 F N5 O6

SOURCE – Welfide.

REFERENCES

1. Akahoshi, F. et al. (Welfide Corp.) *Novel heterocyclic amide cpds. and medicinal uses thereof*. EP 0940400, US 6080738, WO 9818794.
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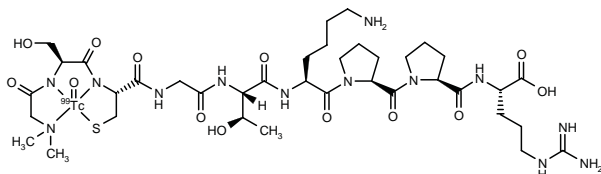
*Identified compound **266115** (see **265122**) Drug Data Rep 1998, 020(08): 0682.

Tc-99m-RP-128

217951

(*SP-5-25*)-Hydrogen [*N,N*-dimethylglycyl- κ *N*-L-seryl- κ *N*-L-cysteinyl- κ *N*, κ *S*-glycyl-L-threonyl-L-lysyl-L-prolyl-L-prolyl-L-argininato(4-)]oxotechnetate(1-)-^{99m}Tc

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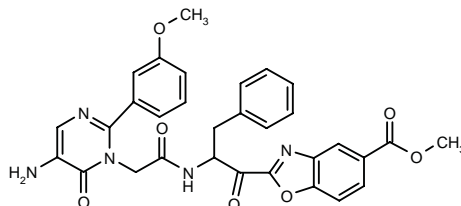
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PHARMACOLOGICAL TOOLS

Y-40079*

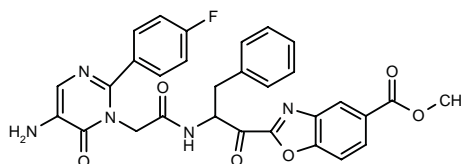
266115

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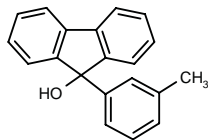
*Identified compound **266115** (see **265122**) Drug Data Rep 1998, 020(08): 0682.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

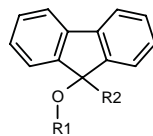
300840

9-(3-Methylphenyl)-9H-fluoren-9-ol



C20 H16 O; Mol wt: 272.3454

ACTION – Agent for the treatment of pain, epilepsy and conditions or diseases associated with increased muscle contraction such as spasticity, an inhibitor of glycine transport that acts by inhibiting the glycine transporter-2 (GlyT-2). Other exemplified compounds from this series of tricyclic derivatives include the following:



Compound	R1	R2	Formula
300841	H	5-Me-2-thienyl	C ₁₈ H ₁₄ OS
300842	H	3-Cl-Ph	C ₁₉ H ₁₃ ClO
300843	(S)-CH ₂ CH(NH ₂)CO ₂ H	Ph	C ₂₂ H ₁₉ NO ₃

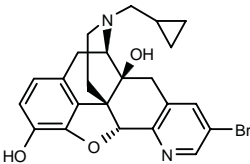
SOURCE – NPS Allelix.

REFERENCES

1. Ognyanov, V.I. et al. (NPS Allelix Corp.) *Tricyclic cpds. as glycine transport inhibitors*. WO 0109117.

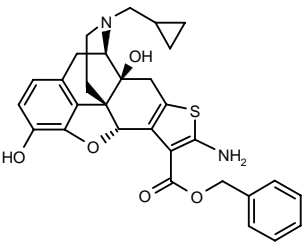
301309

5'-Bromo-17-(cyclopropylmethyl)-4,5 α -epoxy-3,14 β -dihydroxy-6,7-didehydropyrido[2',3':6,7]morphinan



C23 H23 Br N2 O3; Mol wt: 455.3497

ACTION – Potent and selective delta opioid receptor antagonist, as demonstrated in binding assays by K_i values of 1.2 ± 0.13, 15.5 ± 1.0 and 55.7 ± 7.0 nM, respectively, for delta (rat brain), mu (rat brain) and kappa1 (guinea pig brain) receptors. Potentially useful as an analgesic, immunomodulator and for the treatment of drug abuse. Another compound from this series of naltrexone-derived pyridomorphinans and thienomorphinans is:



301310: C30 H30 N2 O5 S

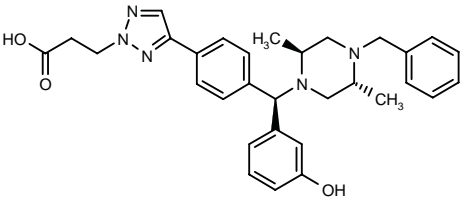
SOURCE – Southern Research Institute, Birmingham, AL (US).

REFERENCES

1. Ananthan, S. (Southern Research Institute) *Pyridomorphinans, thienomorphinans and use thereof*. WO 0112197.

302000

3-[4-[4-[1(R)-[(2S,5R)-4-Benzyl-2,5-dimethylpiperazin-1-yl]-1-(3-hydroxyphenyl)methyl]phenyl]-2H-1,2,3-triazol-2-yl]propionic acid



C31 H35 N5 O3; Mol wt: 525.6495

ACTION – Delta opioid receptor agonist with potential for the treatment and prevention of inflammatory diseases such as arthritis, psoriasis, asthma and inflammatory bowel disease, disorders of respiratory function, gastrointestinal disorders such as irritable bowel syndrome, functional diarrhea, functional distension and nonulcerogenic dyspepsia, and urogenital tract disorders such as incontinence, as well as for use as an analgesic for treating pain including nonsomatic pain, or as an immunosuppressant to prevent rejection in organ transplantation and skin grafts.

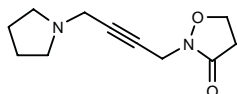
SOURCE – Pfizer.

REFERENCES

1. Maw, G.N. and Middleton, D.S. (Pfizer Inc.) *Cpds. as delta opioid agonists*. US 6200978.

303217

2-[4-(1-Pyrrolidiny)-2-butynyl]isoxazolidin-3-one



C11 H16 N2 O2; Mol wt: 208.2594

ACTION – Analgesic agent, an oxotremorine derivative with *in vitro* functional agonist activity at muscarinic M₁, M₂ and M₃ receptors (pD₂ = 7-8) and strong *in vivo* analgesic activity in both neurogenic and inflammatory pain models such as the formalin licking test and the writhing test in the mouse (ED₅₀ = 0.101 and 0.072 mg/kg, respectively). Compared to oxotremorine, the compound showed similar analgesic activity, with a 2-fold higher therapeutic ratio and no cardiovascular side effects.

SOURCES – Università degli Studi di Milano, Milano (IT); Università degli Studi di Parma, Parma (IT).

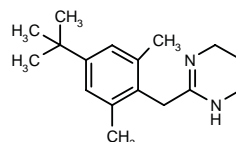
REFERENCES

1. Amstutz, R. et al. *Position 5 at the oxotremorinic skeleton as the steering position for activity at the muscarinic receptors*. *Helv Chim Acta* 1987, 70: 2232.
2. Barocelli, E. et al. *Evidence for specific analgesic activity of a muscarinic agonist selected among a new series of acetylenic derivatives*. *Life Sci* 2001, 68(15): 1775.
3. Barocelli, E. et al. *New analogues of oxotremorine and oxotremorine-M estimation of their in vitro affinity and efficacy at muscarinic receptor subtypes*. *Life Sci* 2000, 67: 717.
4. Conti, P. et al. *Synthesis and binding affinity of new muscarinic ligands structurally related to oxotremorine*. *Bioorg Med Chem Lett* 1997, 7(8): 1033.
5. Dallanoce, C. et al. *Synthesis and functional characterization of novel derivatives related to oxotremorine and oxotremorine-M*. *Bioorg Med Chem* 1999, 7(8): 1539.

ANTIMIGRAINE DRUGS

302825

2-(4-*tert*-Butyl-2,6-dimethylbenzyl)-1,4,5,6-tetrahydropyrimidine



C17 H26 N2; Mol wt: 258.4064

ACTION – Potent and selective 5-HT_{1D} receptor ligand (K_i = 27 and 4370 nM for 5-HT_{1D} and 5-HT_{1B} receptors, respectively) potentially useful for the treatment of migraine.

SOURCES – NPS Allelix; Virginia Commonwealth University, Richmond, VA (US).

REFERENCES

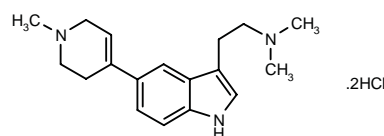
1. Glennon, R.A. and Law, H. (NPS Allelix Corp.; Virginia Commonwealth University) *Imidazoles with serotonin receptor binding activity*. US 5969137, WO 9812183.
2. Prisinzano, T. et al. *Imidazoline-modified benzylimidazolines as h5-HT_{1D/1B} serotonergic ligands*. *Bioorg Med Chem* 2001, 9(3): 613.

ALX-646CL *

266174

N,N-Dimethyl-*N*-[2-[5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-3-yl]ethyl]amine dihydrochloride

ALX-0646 (free base)



C18 H25 N3 . 2HCl; Mol wt: 356.3383

ACTION – 5-HT_{1D} agonist (ED₅₀ = 0.75 μM for contracting isolated rabbit saphenous vein) proven to block neurogenic inflammation via inhibition of protein extravasation in the guinea pig trigeminal extravasation assay with an ED₅₀ value of 1.03 nmol/kg, compared to 3.3 nmol/kg for sumatriptan. Potentially useful for the treatment of migraine. Compound is undergoing phase II studies for the treatment of migraine.

SOURCES – Forest; NPS Allelix.

REFERENCES

1. Slassi, A. et al. (NPS Allelix Corp.) *5-Cyclo indole cpds. as 5-HT_{1D} receptor ligands*. EP 0944595, JP 2001504501, WO 9823587.
2. Slassi, A. et al. (NPS Allelix Corp.) *5-Cyclo indole cpds*. US 5998438.
3. Arora, J. et al. *5-Bicyclopiperidinetryptamine derivatives as selective 5-HT_{1D} agonists*. *Soc Neurosci Abst* 2000, 26(Part 1): Abst 145.14.

4. *ALX-0646 development accelerated.* DailyDrugNews.com (Daily Essentials) 1998, July 24.

5. *Allelix adds two neuropharmaceutical development programs in Q2 1997.* DailyDrugNews.com (Daily Essentials) 1997, April 25.

6. *Allelix gets go-ahead to start U.K. trials for antimigraine drug.* DailyDrugNews.com (Daily Essentials) 1998, April 17.

7. *Allelix presents third-quarter highlights.* DailyDrugNews.com (Daily Essentials) 1999, July 16.

8. *Allelix: Q1 1998 highlights.* DailyDrugNews.com (Daily Essentials) 1998, Jan 28.

9. *Allelix: Q2 1999 highlights.* DailyDrugNews.com (Daily Essentials) 1999, April 28.

10. *Company Profile: Allelix.* DailyDrugNews.com (Daily Essentials) 1999, Feb 22.

11. *Forest signs agreement with NPS Allelix for migraine therapy.* DailyDrugNews.com (Daily Essentials) 2000, Sept 4.

12. *Patient dosing begins in trial of Allelix's selective serotonin agonist.* DailyDrugNews.com (Daily Essentials) 1998, April 30.

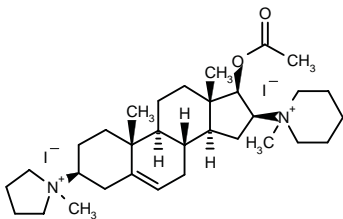
*Identified compound **266174** Drug Data Rep 1998, 020(08): 0658.

ADJUNCTS TO ANESTHESIA

DPJ-489

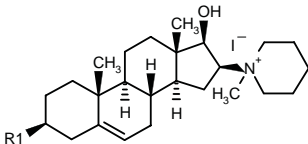
303465

(3β,16β,17β)-17-Acetoxy-16-(1-methylpiperidinium-1-yl)-3-(1-methylpyrrolidinium-1-yl)androst-5-ene diiodide



C32 H54 I2 N2 O2; Mol wt: 752.5906

ACTION – Neuromuscular blocking agent able to reduce the twitch response to nerve stimulation in isolated chicken biventer cervicis muscle preparations (pA₂ = 7.6 and K_d = 25 nM). For comparison, *d*-tubocurarine showed a pA₂ of 6.0 and a K_d value of 1.1 μM. In anesthetized cats, compound at dose of 150 μg/kg produced a reduction of twitch tension in the tibialis anterior and soleus muscles induced by stimulation of the sciatic nerve. Other related compounds are:



Compound	R1	Formula
DPJ-471 [303464]	1-Me-1-pyrrolidiniumyl	C ₃₀ H ₅₂ I ₂ N ₂ O
DPJ-464 [303942]	OH	C ₂₅ H ₄₂ INO ₂

SOURCES – Panjab University, Chandigarh (IN); University of Strathclyde, Glasgow (GB).

REFERENCES

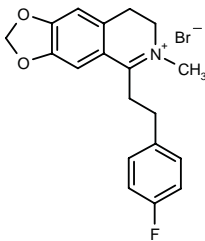
1. Jindal, D.P. et al. *Synthesis and neuromuscular blocking activity of 16β-piperidinosteroidal derivatives.* Eur J Med Chem 2001, 36(2): 195.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

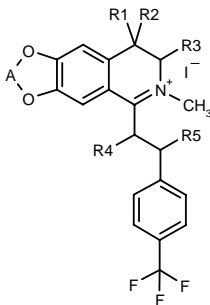
300952

5-[2-(4-Fluorophenyl)ethyl]-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium bromide



C19 H19 Br F N O2; Mol wt: 392.2661

ACTION – Anxiolytic agent proven active in the light–dark transition model in mice, where it exhibited a minimum effective dose (MED) of 1 mg/kg i.p. Compound caused no impairment in spontaneous motor activity in mice (ID₅₀ > 100 mg/kg p.o. vs. 18.4 mg/kg p.o. for diazepam) and exhibited negligible effects on hepatic drug metabolism enzymes such as CYP1A. Within this series of isoquinoline derivatives, the following compounds are also included:



Compound	R1	R2	R3	R4	R5	A	Formula
300953	Pr	bond	H	H	H	-(CH2)2-	C ₂₄ H ₂₅ F ₃ INO ₂
300954	H	bond	bond	bond	bond	-CH2-	C ₂₀ H ₁₅ F ₃ INO ₂
300960	Pr	H	H	H	H	-(CH2)2-	C ₂₄ H ₂₇ F ₃ INO ₂

4. *ALX-0646 development accelerated.* DailyDrugNews.com (Daily Essentials) 1998, July 24.

5. *Allelix adds two neuropharmaceutical development programs in Q2 1997.* DailyDrugNews.com (Daily Essentials) 1997, April 25.

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9. *Allelix: Q2 1999 highlights.* DailyDrugNews.com (Daily Essentials) 1999, April 28.

10. *Company Profile: Allelix.* DailyDrugNews.com (Daily Essentials) 1999, Feb 22.

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12. *Patient dosing begins in trial of Allelix's selective serotonin agonist.* DailyDrugNews.com (Daily Essentials) 1998, April 30.

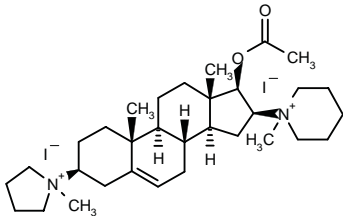
*Identified compound **266174** Drug Data Rep 1998, 020(08): 0658.

ADJUNCTS TO ANESTHESIA

DPJ-489

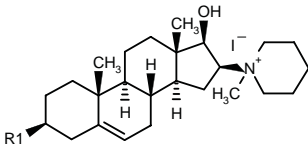
303465

(3β,16β,17β)-17-Acetoxy-16-(1-methylpiperidinium-1-yl)-3-(1-methylpyrrolidinium-1-yl)androst-5-ene diiodide



C32 H54 I2 N2 O2; Mol wt: 752.5906

ACTION – Neuromuscular blocking agent able to reduce the twitch response to nerve stimulation in isolated chicken biventer cervicis muscle preparations (pA₂ = 7.6 and K_d = 25 nM). For comparison, *d*-tubocurarine showed a pA₂ of 6.0 and a K_d value of 1.1 μM. In anesthetized cats, compound at dose of 150 μg/kg produced a reduction of twitch tension in the tibialis anterior and soleus muscles induced by stimulation of the sciatic nerve. Other related compounds are:



Compound	R1	Formula
DPJ-471 [303464]	1-Me-1-pyrrolidiniumyl	C ₃₀ H ₅₂ I ₂ N ₂ O
DPJ-464 [303942]	OH	C ₂₅ H ₄₂ INO ₂

SOURCES – Panjab University, Chandigarh (IN); University of Strathclyde, Glasgow (GB).

REFERENCES

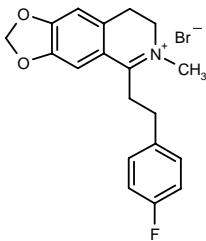
1. Jindal, D.P. et al. *Synthesis and neuromuscular blocking activity of 16β-piperidinosteroidal derivatives.* Eur J Med Chem 2001, 36(2): 195.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

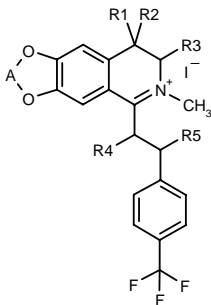
300952

5-[2-(4-Fluorophenyl)ethyl]-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium bromide

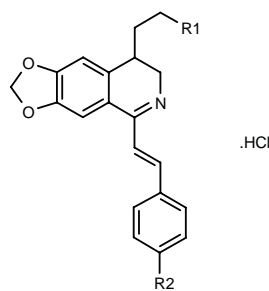


C19 H19 Br F N O2; Mol wt: 392.2661

ACTION – Anxiolytic agent proven active in the light–dark transition model in mice, where it exhibited a minimum effective dose (MED) of 1 mg/kg i.p. Compound caused no impairment in spontaneous motor activity in mice (ID₅₀ > 100 mg/kg p.o. vs. 18.4 mg/kg p.o. for diazepam) and exhibited negligible effects on hepatic drug metabolism enzymes such as CYP1A. Within this series of isoquinoline derivatives, the following compounds are also included:



Compound	R1	R2	R3	R4	R5	A	Formula
300953	Pr	bond	H	H	H	-(CH2)2-	C ₂₄ H ₂₅ F ₃ INO ₂
300954	H	bond	bond	bond	bond	-CH2-	C ₂₀ H ₁₅ F ₃ INO ₂
300960	Pr	H	H	H	H	-(CH2)2-	C ₂₄ H ₂₇ F ₃ INO ₂



Compound	R1	R2	Formula
300955	Et	CF3	C ₂₃ H ₂₂ F ₃ NO ₂ .HCl
300956	Me	CF3	C ₂₂ H ₂₀ F ₃ NO ₂ .HCl
300957	H	OMe	C ₂₁ H ₂₁ NO ₃ .HCl
300958	Bu	CF3	C ₂₅ H ₂₆ F ₃ NO ₂ .HCl
300959	Et	OMe	C ₂₃ H ₂₅ NO ₃ .HCl

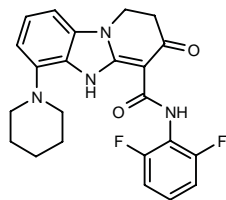
SOURCE – Egis.

REFERENCES

1. Domán, I. et al. (Egis Pharmaceuticals Ltd.) *Isoquinoline derivs., pharmaceutical compsns. containing the same, and a process for the preparation of the active substance.* WO 0109101.

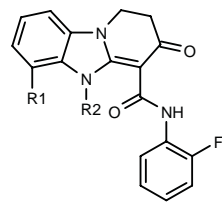
301056

N-(2,6-Difluorophenyl)-3-oxo-6-(1-piperidiny)-1,2,3,5-tetrahydropyrido[1,2-a]benzimidazole-4-carboxamide



C23 H22 F2 N4 O2; Mol wt: 424.4488

ACTION – Compound with affinity for the benzodiazepine site on GABA_A receptors (IC₅₀ = 0.41 nM), proven active in inhibiting metrazole-induced convulsions in mice (ED₅₀ = 3.64 mg/kg p.o.) and to exhibit anxiolytic activity in a rat conflict test (MED = 3 mg/kg p.o.). Potentially useful for the treatment of CNS disorders such as anxiety, convulsions, depression, sleeplessness, muscle spasms, attention deficit hyperactivity disorder and benzodiazepine overdose. Other specifically claimed substituted pyrido[1,2-a]benzimidazole derivatives are:



Compound	R1	R2	Formula
301057	1,4-dioxo-8-azaspiro[4.5]decan-8-yl	H	C ₂₅ H ₂₅ FN ₄ O ₄
301058	4-oxo-1-Pip	H	C ₂₃ H ₂₁ FN ₄ O ₃
301059	1,4-dioxo-8-azaspiro[4.5]decan-8-yl	Me	C ₂₆ H ₂₇ FN ₄ O ₄
301060	1-imidazolyl	H	C ₂₁ H ₁₆ FN ₅ O ₂
301061	1-imidazolyl	Me	C ₂₂ H ₁₈ FN ₅ O ₂
301062	1-Piz	Me	C ₂₃ H ₂₄ FN ₅ O ₂
301063	4-(MeOCH2CO)-1-Piz	Me	C ₂₆ H ₂₈ FN ₅ O ₄

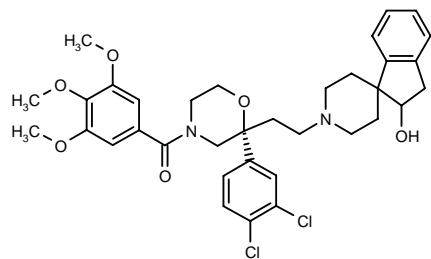
SOURCE – Ortho-McNeil.

REFERENCES

1. Reitz, A.B. et al. (Ortho-McNeil Pharmaceutical, Inc.) *C-6 ring-substd. pyrido[1,2-a]-benzimidazole derivs. useful in treating central nervous system disorders.* WO 0109132.

301492

1-[2(R)-(3,4-Dichlorophenyl)-2-[2-[2-hydroxyspiro[indane-1,4'-piperidin]-1'-yl]ethyl]morpholin-4-yl]-1-(3,4,5-trimethoxyphenyl)methanone



C35 H40 Cl2 N2 O6; Mol wt: 655.6150

ACTION – Potent tachykinin NK₁, NK₂ and NK₃ receptor antagonist, as demonstrated by IC₅₀ values of 12, 4.4 and 2.3 ng/ml, respectively in binding assays using guinea pig lung, ileum and brain membrane preparations. Potentially useful for the treatment of tachykinin-mediated disorders such as CNS, respiratory, inflammatory, allergic, ocular, immune and gastrointestinal disorders. A representative compound from a series of spiro piperidine derivatives.

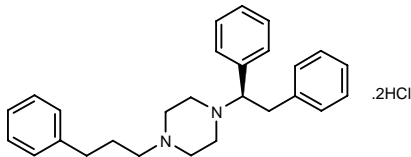
SOURCE – Sankyo.

REFERENCES

1. Nishi, T. et al. (Sankyo Co., Ltd.) *Medicines containing spiro piperidine derivs.* JP 2001031570.

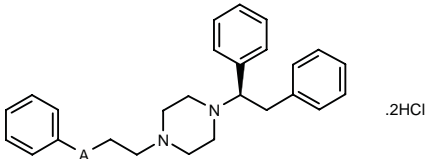
301598

1-[1(*R*),2-Diphenylethyl]-4-(3-phenylpropyl)piperazine dihydrochloride



C27 H32 N2 . 2HCl; Mol wt: 457.4856

ACTION – Agent for the treatment of anxiety and dystonia, a selective σ_2 receptor ligand, as demonstrated in binding assays by IC₅₀ values of 0.013 and 28 nM for σ_2 and σ_1 receptors from rat and guinea pig brain homogenates, respectively (ratio σ_1/σ_2 = 2,200). Other compounds from this series of 1,4-disubstituted piperazine derivatives include the following:



Compound	A	Formula
301599	-CH2CH2-	C ₂₈ H ₃₄ N ₂ .2HCl
301600	bond	C ₂₆ H ₃₀ N ₂ .2HCl

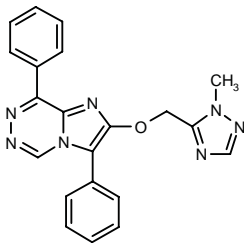
SOURCE – Santen.

REFERENCES

1. Mita, S. et al. (Santen Pharmaceutical Co., Ltd.) *Selective ligand for σ_2 receptor*. JP 2001026584.

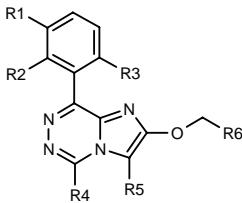
301737

2-(1-Methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3,8-diphenylimidazo[1,2-*d*][1,2,4]triazine



C21 H17 N7 O; Mol wt: 383.4133

ACTION – Agent for the treatment or prevention of CNS disorders, particularly anxiety, with potent and selective affinity for the α_2 and/or α_3 subunits of the human GABA_A receptor (K_i = 100 nM or less). Other specifically claimed compounds from this series of substituted imidazo[1,2-*d*]-[1,2,4]triazine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
301738	F	H	F	H	Ph	1-Me-1,2,4-triazol-5-yl	C ₂₁ H ₁₅ F ₂ N ₇ O
301740	H	H	F	H	cyclobutyl	1-Me-1,2,4-triazol-5-yl	C ₁₉ H ₁₈ FN ₇ O
301742	H	H	F	Me	Ph	1-Me-1,2,4-triazol-5-yl	C ₂₂ H ₁₈ FN ₇ O
301743	H	H	H	Et	cyclopentyl	1-Et-1,2,4-triazol-5-yl	C ₂₃ H ₂₇ N ₇ O
301744	H	F	F	Me	cyclopentyl	1-Me-1,2,4-triazol-5-yl	C ₂₁ H ₂₁ F ₂ N ₇ O
301745	H	H	F	Me	cyclopentyl	1-Me-1,2,3-triazol-5-yl	C ₂₁ H ₂₂ FN ₇ O
301746	H	H	F	Me	cyclopentyl	1-Me-1,2,4-triazol-3-yl	C ₂₁ H ₂₂ FN ₇ O
301747	H	H	H	Me	2-thienyl	1-Et-1,2,4-triazol-5-yl	C ₂₁ H ₁₉ N ₇ OS

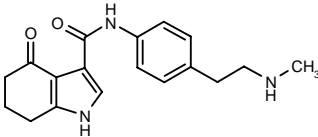
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Imidazo-triazine derivs. as ligands for GABA receptors*. WO 0114377.

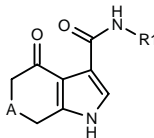
301982

N-[4-[2-(Methylamino)ethyl]phenyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide



C18 H21 N3 O2; Mol wt: 311.3829

ACTION – Agent for the treatment of anxiety, depression, sleep disorders, cognitive impairment and Alzheimer's disease with high and selective affinity for the benzodiazepine binding site on the GABA_A receptor (K_i = 0.24 nM against [³H]-flumazenil binding in rat cortex homogenates). Other exemplified compounds from this series of fused pyrrolecarboxamides include the following:



Compound	R1	A	Formula
301984	3-(MeNHCH2)-Ph	-CH2-	C ₁₇ H ₁₉ N ₃ O ₂
301985	4-(MeOCH2CH2O)-Ph	-CH2-	C ₁₈ H ₂₀ N ₂ O ₄
301986	2-F-4-(MeNHCH2)-Ph	-CH2-	C ₁₇ H ₁₈ FN ₃ O ₂
301987	4-(cyclopropyl-NHCH2)-Ph	-CH2-	C ₁₉ H ₂₁ N ₃ O ₂
301988	4-(NH2CH2)-Ph	-CH2-	C ₁₆ H ₁₇ N ₃ O ₂
301989	4-(MeNHCH2)-Ph	-(CH2)2-	C ₁₈ H ₂₁ N ₃ O ₂
301990	3-(CH2OH)-Ph	-C(Me)2-	C ₁₈ H ₂₀ N ₂ O ₃
301991	4-(HOCH2CH2O)-Ph	-CH(Me)-	C ₁₈ H ₂₀ N ₂ O ₄
301992	1,3-benzodioxol-5-yl	-CH2-	C ₁₆ H ₁₄ N ₂ O ₄
301993	1,4-benzodioxan-6-yl	-CH2-	C ₁₇ H ₁₆ N ₂ O ₄
301994	1,4-benzodioxan-6-yl	-(CH2)2-	C ₁₈ H ₁₈ N ₂ O ₄
301995	2,3-dihydro-6-indolyl	-CH2-	C ₁₇ H ₁₇ N ₃ O ₂
301996	6-(HOCH2CH2O)-3-Pyr	-CH2-	C ₁₆ H ₁₇ N ₃ O ₄
301997	6-(HOCH2CH2O)-3-Pyr	-CH(Me)-	C ₁₇ H ₁₉ N ₃ O ₄

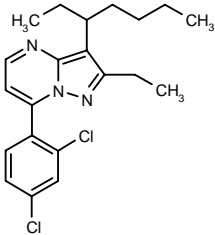
SOURCE – Neurogen.

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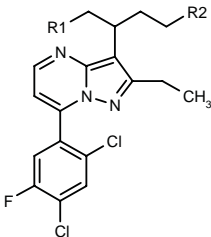
302146

7-(2,4-Dichlorophenyl)-2-ethyl-3-(1-ethylpentyl)pyrazolo-[1,5-*a*]pyrimidine



C21 H25 Cl2 N3; Mol wt: 390.3555

ACTION – Potential anxiolytic agent and antidepressant, a high-affinity ligand for the corticotropin-releasing factor receptor CRF₁ (K_i = 0.35 nM). Other heterocyclic compounds with aryl substitution are:



Compound	R1	R2	Formula
302144	H	Me	C ₁₉ H ₂₀ Cl ₂ FN ₃
302145	Me	H	C ₁₉ H ₂₀ Cl ₂ FN ₃

SOURCE – DuPont Pharmaceuticals.

REFERENCES

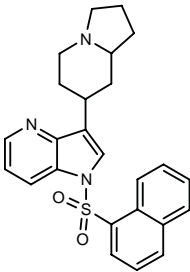
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2. Wilde, R.G. et al. *Non-peptide CRF1 antagonists: Pyrazolo[1,5-*a*]pyrimidines and pyrazolo[5,1-*c*][1,2,3]triazines*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 95.

ANTIPSYCHOTIC DRUGS

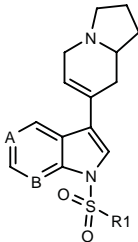
300767

1-(1-Naphthylsulfonyl)-3-(perhydroindolizin-7-yl)-1*H*-pyrrolo[3,2-*b*]pyridine



C25 H25 N3 O2 S; Mol wt: 431.5575

ACTION – Selective 5-HT₆ receptor antagonist that showed > 90% inhibition of the 5-HT₆ receptor and < 10% inhibition of 5-HT_{2A}, 5-HT_{2C} and 5-HT₇ receptors in *in vitro* binding assays. This compound is indicated for the treatment or prevention of CNS disturbances, particularly schizophrenia. Other exemplified azaindoles include the following:



Compound	R1	A	B	Formula
300768	Ph	N	CH	C ₂₁ H ₂₁ N ₃ O ₂ S
300769	2-Naph	CH	N	C ₂₆ H ₂₃ N ₃ O ₂ S

SOURCE – NPS Allelix.

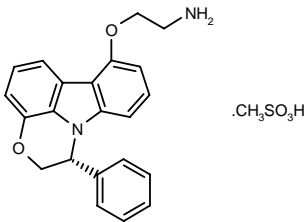
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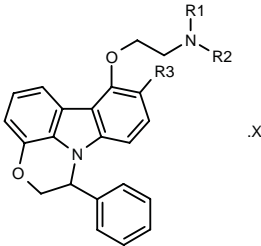
300865

(–)-2-[1(*R*)-Phenyl-1,2-dihydro[1,4]oxazino[2,3,4-*jk*]-carbazol-7-yloxy]ethylamine methanesulfonate



C22 H20 N2 O2 . C H4 O3 S; Mol wt: 440.5176

ACTION – Agent for the treatment of CNS disorders such as psychotic diseases, a 5-HT₆ receptor modulator (K_i = 1.8 nM against [³H]-LSD binding to human 5-HT₆ receptors cloned in HeLa cells). Other specifically claimed compounds from this series of oxazinocarbazoles include the following:



Compound	R1	R2	R3	X	Formula
300867	H	H	H	MeSO3H	C ₂₂ H ₂₀ N ₂ O ₂ .CH ₄ O ₃ S
300869	Me	H	H	fumarate	C ₂₃ H ₂₂ N ₂ O ₂ .C ₄ H ₄ O ₄
300870	H	H	Cl	MeSO3H	C ₂₂ H ₁₉ ClN ₂ O ₂ .CH ₄ O ₃ S
300871	-CH2CH2N(Me)CH2CH2-	H	H		C ₂₇ H ₂₉ N ₃ O ₂
300872	CH2CH2OH	H	H		C ₂₄ H ₂₄ N ₂ O ₃

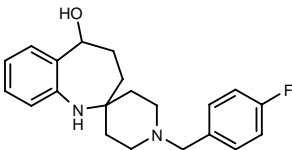
SOURCE – Pharmacia.

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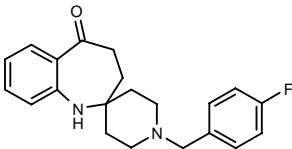
301314

1'-(4-Fluorobenzyl)spiro[2,3,4,5-tetrahydro-1H-1-benzazepine-2,4'-piperidine]-5-ol



C21 H25 F N2 O; Mol wt: 340.4395

ACTION – Agent with affinity for various cellular receptors, particularly σ receptors, potentially useful in the treatment of psychosis, depression, pain, multiple sclerosis, anxiety, stroke, motor neuron diseases and glaucoma. *In vitro*, compound gave IC₅₀ values of < 10, < 100, < 1000, > 1000 and < 1000 for guinea pig and human σ₁, rat σ₂ and human 5-HT_{2A} and 5-HT_{2B} receptors, respectively. In addition, it was shown to reduce MK-801-induced locomotion and stereotypies in rats at 1 mg/kg i.p. and exhibited some anxiolytic activity in the elevated plus-maze test in rats at 5 mg/kg p.o. Another compound from this series of spirocyclic derivatives is:



301315: C21 H23 F N2 O

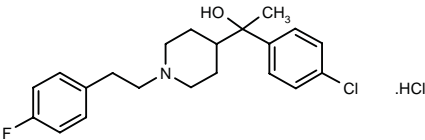
SOURCE – Sepracor.

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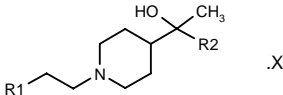
301789

1-(4-Chlorophenyl)-1-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]ethanol hydrochloride



C21 H25 Cl F N O . HCl; Mol wt: 398.3464

ACTION – 5-HT_{2A} receptor antagonist (IC₅₀ = 1.3 nM against [³H]-ketanserin binding in rat frontal cortex homogenates) proven to potently inhibit DOI-induced head twitches in mice following oral administration. Potentially useful for the treatment of psychoses, schizophrenia, depression, neurological disorders, impaired memory, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders, premenstrual syndrome and obsessive-compulsive disorders. Other exemplified compounds from this series of piperidine alcohols include the following:



Compound	R1	R2	X	Formula
301790	5-Cl-2-thienyl	4-F-Ph	HCl	C ₁₉ H ₂₃ ClFNO ₃ .HCl
301791	4-F-Ph	5-Cl-2-thienyl		C ₁₉ H ₂₃ ClFNO ₃
301792	5-Cl-2-thienyl	4-Cl-Ph	HCl	C ₁₉ H ₂₃ Cl ₂ NO ₃ .HCl
301793	4-F-Ph	1,4-benzodioxan-5-yl	HCl	C ₂₃ H ₂₈ FNO ₃ .HCl
301794	4-F-Ph	4-CF3-Ph	HCl	C ₂₂ H ₂₅ F ₄ NO ₃ .HCl

SOURCE – Merck KGaA.

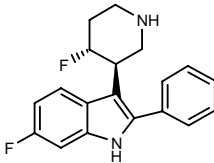
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L-838751

288192

6-Fluoro-3-[4(R)-fluoropiperidin-3(R)-yl]-2-phenyl-1H-indole



C19 H18 F2 N2; Mol wt: 312.3612

ACTION – Potent and selective 5-HT_{2A} receptor antagonist with subnanomolar affinity for 5-HT_{2A} receptors (K_i = 0.06 nM), 50- and 100-fold selectivity over α_1 -adrenoceptors and 5-HT_{2C} receptors, respectively, and very low affinity for dopamine D2 receptors. The antagonist activity of compound was demonstrated in functional experiments in CHO cells expressing 5-HT_{2A} receptors, where it showed no intrinsic activity. Pharmacokinetic experiments in dogs and rats showed good oral availability (33-80%) and a long plasma half-life (6.4-12 h). Potentially useful for the treatment of schizophrenia.

SOURCE – Merck Sharp & Dohme.

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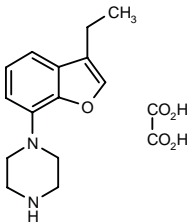
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TREATMENT OF MOOD
DISORDERS

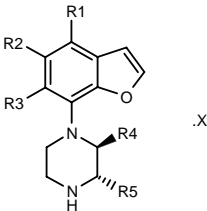
300895

1-(3-Ethyl-1-benzofuran-7-yl)piperazine oxalate



C14 H18 N2 O . C2 H2 O4; Mol wt: 320.3430

ACTION – Agent for the treatment of obesity and depression, a selective 5-HT_{2C} receptor agonist. Other exemplified compounds from this series of benzofuryl-piperazines and benzofurylhomopiperazines include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
300896	Me	Cl	Me	H	H	oxalate	C ₁₄ H ₁₇ ClN ₂ O.C ₂ H ₂ O ₄
300899	Me	F	H	H	H	oxalate	C ₁₃ H ₁₅ FN ₂ O.C ₂ H ₂ O ₄
300900	F	F	F	H	Me	HCl	C ₁₃ H ₁₃ F ₃ N ₂ O.HCl
300901	H	F	H	Me	H	fumarate	C ₁₃ H ₁₅ FN ₂ O.C ₄ H ₄ O ₄
300906	H	F	H	CH(Me)Et	H	fumarate	C ₁₆ H ₂₁ FN ₂ O.C ₄ H ₄ O ₄
300910	H	CH ₂ OH	H	H	H	HCl	C ₁₃ H ₁₆ N ₂ O ₂ .HCl
300911	H	CO ₂ Me	H	H	H	HCl	C ₁₄ H ₁₆ N ₂ O ₃ .HCl

Compound	R1	R2	R3	R4	R5	X	Formula
300912	F	F	F	H	Me	oxalate	C ₁₃ H ₁₃ F ₃ N ₂ O.C ₂ H ₂ O ₄
300913	H	F	H	H	Et	fumarate	C ₁₄ H ₁₇ FN ₂ O.C ₄ H ₄ O ₄
300914	F	F	H	Me	H	fumarate	C ₁₃ H ₁₄ F ₂ N ₂ O.C ₄ H ₄ O ₄

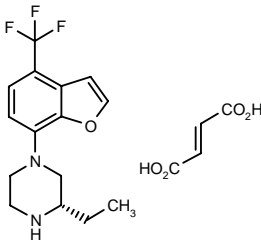
SOURCE – Lilly.

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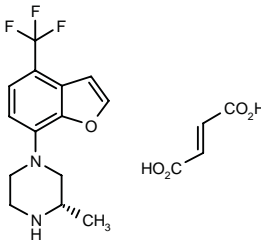
300916

3(S)-Ethyl-1-[4-(trifluoromethyl)-1-benzofuran-7-yl]piperazine fumarate



C15 H17 F3 N2 O . C4 H4 O4; Mol wt: 414.3779

ACTION – Agent for the treatment of obesity and depression, a potent and selective 5-HT_{2C} receptor agonist, as demonstrated in binding assays by a K_i value of 0.77 nM for 5-HT_{2c} receptors compared to K_i values of 261, 2937, 726, 1143, 1000, 27.76, 177.03 and 607 nM, respectively, for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B} and 5-HT₆ receptors. Agonist activity at 5-HT_{2C} receptors was demonstrated in a [³⁵S]-GTP γ binding assay by an EC₅₀ value of 7.8 nM. Another specifically claimed compound from this series of benzofuryl-piperazines is:



300917: C14 H15 F3 N2 O . C4 H4 O4

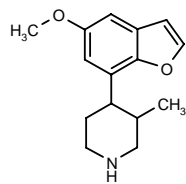
SOURCE – Lilly.

REFERENCES

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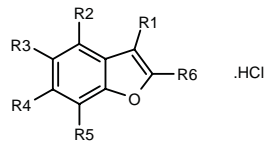
300918

(±)-4-(5-Methoxy-1-benzofuran-7-yl)-3-methylpiperidine

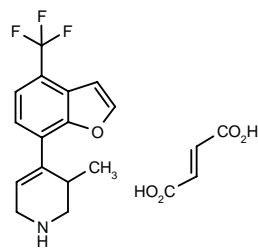


C15 H19 N O2; Mol wt: 245.3201

ACTION – Agent for the treatment of obesity and depression, a selective 5-HT_{2C} receptor agonist. Other exemplified compounds from this series of benzofurans include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
300920	H	H	CF3	H	cis-3-Me-4-Pip	H	C ₁₅ H ₁₆ F ₃ NO.HCl
300921	H	cis-3-Me-4-Pip	F	H	H	H	C ₁₄ H ₁₆ FNO.HCl
300922	H	H	F	H	3,3-(Me)2-4-Pip	H	C ₁₅ H ₁₆ FNO.HCl
300923	H	H	F	H	cis-3-Me-4-Pip	H	C ₁₄ H ₁₆ FNO.HCl
300924	Cl	H	F	H	cis-3-Me-4-Pip	H	C ₁₄ H ₁₅ ClFNO.HCl
300925	H	H	Cl	H	cis-3-Me-4-Pip	H	C ₁₄ H ₁₆ ClNO.HCl
300926	H	F	H	F	cis-3-Me-4-Pip	H	C ₁₄ H ₁₅ F ₂ NO.HCl
300927	H	H	H	H	cis-3-Me-4-Pip	Me	C ₁₅ H ₁₉ NO.HCl
300928	H	H	H	F	cis-3-Me-4-Pip	H	C ₁₄ H ₁₆ FNO.HCl



300919: C15 H14 F3 N O . C4 H4 O4

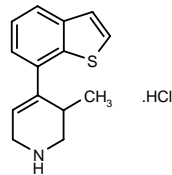
SOURCE – Lilly.

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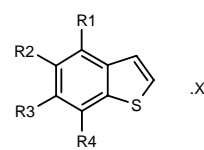
300929

4-(1-Benzothien-7-yl)-3-methyl-1,2,3,6-tetrahydropyridine hydrochloride



C14 H15 N S . HCl; Mol wt: 265.8064

ACTION – Agent for the treatment of obesity and depression, a selective 5-HT_{2C} receptor agonist. Other exemplified compounds from this series of benzothiophenes include the following:



Compound	R1	R2	R3	R4	X	Formula
300931	H	H	H	5-Me-1,2,3,6-tetrahydro-4-Pyr	oxalate	C ₁₄ H ₁₅ NS .C ₂ H ₂ O ₄
300932	H	H	H	3,3-(Me)2-1,2,3,6-tetrahydro-4-Pyr	HCl	C ₁₅ H ₁₇ NS .HCl
300933	F	H	H	3,3-(Me)2-1,2,3,6-tetrahydro-4-Pyr	HCl	C ₁₅ H ₁₆ FNS .HCl
300934	H	H	F	cis-3-Me-4-Pip	oxalate	C ₁₄ H ₁₆ FNS .C ₂ H ₂ O ₄
300935	H	H	H	cis-3-Et-4-Pip	HCl	C ₁₅ H ₁₉ NS .HCl
300936	H	F	H	cis-3-Me-4-Pip	HCl	C ₁₄ H ₁₆ FNS .HCl
300937	H	H	H	cis-3-Me-4-Pip	HCl	C ₁₄ H ₁₇ NS .HCl
300938	H	H	H	3,3-(Me)2-4-Pip	oxalate	C ₁₅ H ₁₉ NS .C ₂ H ₂ O ₄
300939	3-Me-4-Pip	H	H	H	HCl	C ₁₄ H ₁₇ NS .HCl

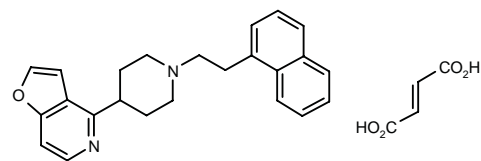
SOURCE – Lilly.

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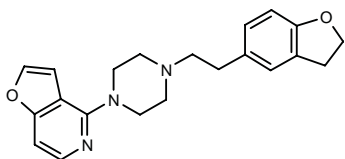
301082

4-[1-[2-(1-Naphthyl)ethyl]piperidin-4-yl]furo[3,2-c]pyridine fumarate



C24 H24 N2 O . C4 H4 O4; Mol wt: 472.5382

ACTION – 5-HT reuptake inhibitor and 5-HT_{1A} antagonist or partial agonist with demonstrated affinity for 5-HT_{1A} receptors in CHO cells and for 5-HT reuptake sites in rat cortical membranes, exhibiting a pK_i > 7.5 in both assays. This compound was active in reducing aggressivity in mice with an ID₅₀ < 1.5 mg/kg i.p. and exhibited anti-depressant-like activity in the marble-burying test in mice with an ID₅₀ of 1.64 mg/kg s.c. Potentially useful for the treatment of depression, anxiety, panic attacks, obsessive–compulsive disorders, phobia and cognition disorders. Another exemplified pyridine derivative is:



301083: C₂₁ H₂₃ N₃ O₂

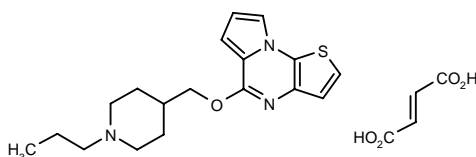
SOURCE – ADIR.

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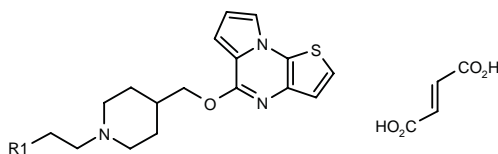
301680

5-(1-Propylpiperidin-4-ylmethoxy)pyrrolo[1,2-*a*]thieno-[3,2-*e*]pyrazine fumarate



C₁₈ H₂₃ N₃ O S . C₄ H₄ O₄; Mol wt: 445.5373

ACTION – Agent for the treatment of depression and memory disorders with high affinity for 5-HT₄ receptors. *In vivo*, compound was shown to significantly antagonize scopolamine-induced memory impairment in mice at 0.5 mg/kg i.p. In addition, it exhibited antidepressant activity in the forced swimming test in mice at 60 mg/kg i.p., being comparable to imipramine at 30 mg/kg i.p., and it also displayed analgesic activity in the hot-plate test in mice at the same dose, being more effective than morphine at 8 mg/kg, while it was devoid of significant anxiolytic activity in the elevated plus-maze test in mice. Compound displayed no significant effects on cardiovascular and hemodynamic parameters in the rat when given i.v. at sublethal doses. Within this series of ether derivatives of pyrrolo[1,2-*a*]quinoxalines, the following compounds are also included:



Compound	R1	Formula
301681	H	C ₁₇ H ₂₁ N ₃ OS.C ₄ H ₄ O ₄
301682	Et	C ₁₉ H ₂₅ N ₃ OS.C ₄ H ₄ O ₄

SOURCE – Université de Caen, Caen Cedex (FR).

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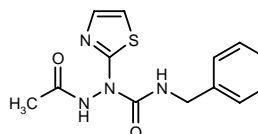
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

302707

2-Acetyl-*N*-benzyl-1-(2-thiazolyl)hydrazinecarboxamide



C₁₃ H₁₄ N₄ O₂ S; Mol wt: 290.3456

ACTION – Anticonvulsant proven to protect against maximal electroshock (MES)-induced seizures in both mice and rats (ED₅₀ = 22 mg/kg i.p and 6.2 mg/kg p.o., respectively), as well as against focal seizures in the hippocampal kindled rat test (ED₅₀ = 56 mg/kg i.p.). Compound exhibited low neurological toxicity in the rotarod assay (TD₅₀ = 120 mg/kg in mice and > 250 mg/kg in rats) and showed a more favorable protective index (TD₅₀/ED₅₀) than phenytoin in mice. In addition, compound provided no significant voltage-dependent blockade of Na⁺ channels in neuroblastoma NIE-115 cells. In comparison, phenytoin induced 48% blockade.

SOURCES – University of Houston, Houston, TX (US); National Institutes of Health, Bethesda, MD (US); University of North Carolina, Chapel Hill, NC (US).

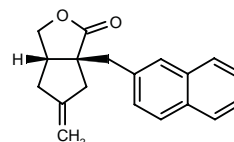
REFERENCES

1. Andurkar, S.V. et al. *Synthesis and structural studies of aza analogues of functionalized amino acids: New anticonvulsant agents*. J Med Chem 2001, 44(9): 1475.

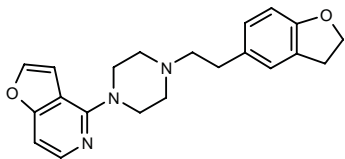
BAY-36-7620*

279058

(3a*S*,6a*S*)-5-Methylene-6a-(naphthalen-2-ylmethyl)perhydrocyclopenta[*c*]furan-1-one



C₁₉ H₁₈ O₂; Mol wt: 278.3492



301083: C21 H23 N3 O2

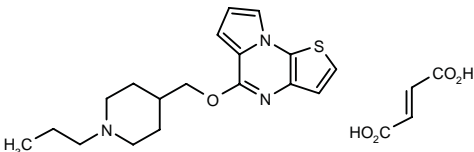
SOURCE – ADIR.

REFERENCES

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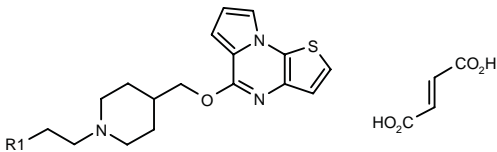
301680

5-(1-Propylpiperidin-4-ylmethoxy)pyrrolo[1,2-*a*]thieno-[3,2-*e*]pyrazine fumarate



C18 H23 N3 O S . C4 H4 O4; Mol wt: 445.5373

ACTION – Agent for the treatment of depression and memory disorders with high affinity for 5-HT₄ receptors. *In vivo*, compound was shown to significantly antagonize scopolamine-induced memory impairment in mice at 0.5 mg/kg i.p. In addition, it exhibited antidepressant activity in the forced swimming test in mice at 60 mg/kg i.p., being comparable to imipramine at 30 mg/kg i.p., and it also displayed analgesic activity in the hot-plate test in mice at the same dose, being more effective than morphine at 8 mg/kg, while it was devoid of significant anxiolytic activity in the elevated plus-maze test in mice. Compound displayed no significant effects on cardiovascular and hemodynamic parameters in the rat when given i.v. at sublethal doses. Within this series of ether derivatives of pyrrolo[1,2-*a*]quinoxalines, the following compounds are also included:



Compound	R1	Formula
301681	H	C ₁₇ H ₂₁ N ₃ OS.C ₄ H ₄ O ₄
301682	Et	C ₁₉ H ₂₅ N ₃ OS.C ₄ H ₄ O ₄

SOURCE – Université de Caen, Caen Cedex (FR).

REFERENCES

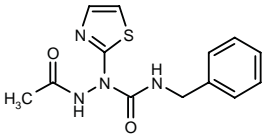
1. Rault, S. et al. (Université de Caen Basse-Normandie) *Ether derivs. of pyrrolo-[1,2-*a*]quinoxalines, method for producing them and their use in therapy.* FR 2797630, WO 0114381.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

302707

2-Acetyl-*N*-benzyl-1-(2-thiazolyl)hydrazinecarboxamide



C13 H14 N4 O2 S; Mol wt: 290.3456

ACTION – Anticonvulsant proven to protect against maximal electroshock (MES)-induced seizures in both mice and rats (ED₅₀ = 22 mg/kg i.p and 6.2 mg/kg p.o., respectively), as well as against focal seizures in the hippocampal kindled rat test (ED₅₀ = 56 mg/kg i.p.). Compound exhibited low neurological toxicity in the rotarod assay (TD₅₀ = 120 mg/kg in mice and > 250 mg/kg in rats) and showed a more favorable protective index (TD₅₀/ED₅₀) than phenytoin in mice. In addition, compound provided no significant voltage-dependent blockade of Na⁺ channels in neuroblastoma NIE-115 cells. In comparison, phenytoin induced 48% blockade.

SOURCES – University of Houston, Houston, TX (US); National Institutes of Health, Bethesda, MD (US); University of North Carolina, Chapel Hill, NC (US).

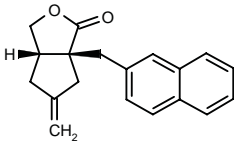
REFERENCES

1. Andurkar, S.V. et al. *Synthesis and structural studies of aza analogues of functionalized amino acids: New anticonvulsant agents.* J Med Chem 2001, 44(9): 1475.

BAY-36-7620*

279058

(3*aS*,6*aS*)-5-Methylene-6*a*-(naphthalen-2-ylmethyl)perhydrocyclopenta[*c*]furan-1-one



C19 H18 O2; Mol wt: 278.3492

ACTION – Potent and selective noncompetitive antagonist at metabotropic glutamate mglu₁ receptors with an IC₅₀ value of 0.16 μM for inhibition of inositol phosphate formation in HEK293 cells expressing the mglu₁ receptor. In this system, compound at 10 μM reduced basal constitutive activity, indicating an inverse agonist property at this receptor. Compound was also seem to block DHPG-activated big K⁺ channels in cerebral granule neuron cultures (IC₅₀ = 200 nM), with no effect against ionotropic glutamate receptors expressed in these cells. *In vivo*, compound was seen to protect mice from seizures induced by pentylenetetrazole (MED = 10 mg/kg i.v.), 3,5-DHPG (ED₅₀ = 71 mg/kg) or sound (ED₅₀ = 33.2 and 163 mg/kg for the tonic and clonic phase, respectively). In addition, compound showed neuroprotective activity in the middle cerebral artery occlusion and SHD model in rats (MED = 0.03 and 0.01 mg/kg i.v., respectively). Only mild behavioral side effects were seen at high (75-200 mg/kg) doses.

SOURCE – Bayer.

REFERENCES

1. Stolle, A. et al. (Bayer AG) *Substd. alpha,beta-anellated butyrolactones*. DE 19801646, EP 1047684, WO 9936416.

2. Carroll, F.Y. et al. *BAY36-7620: A potent non-competitive mGlu1 receptor antagonist with inverse agonist activity*. Mol Pharmacol 2001, 59(5): 965.

3. Carroll, F.Y. et al. *Pharmacological characterisation of BAY 36-7620, a novel antagonist selective for mGluR1 receptors*. Soc Neurosci Abst 2000, 26(Part 2): Abst 618.4.

4. Chapman, A. et al. *Anticonvulsant activity in mice of BAY 36-7620, a novel selective mGluR1 antagonist*. Soc Neurosci Abst 2000, 26(Part 2): Abst 618.11.

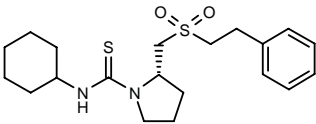
5. Müller, T. et al. *BAY 36-7620, a selective metabotropic glutamate receptor1 antagonist with anticonvulsant and neuroprotective properties*. Soc Neurosci Abst 2000, 26(Part 2): Abst 618.10.

*Identified compound **279058** Drug Data Rep 1999, 021(10): 0872.

THERAPY OF
NEURODEGENERATIVE DISEASES

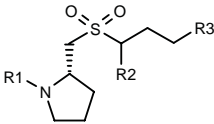
301589

N-Cyclohexyl-2(*S*)-(2-phenylethylsulfonylmethyl)pyrrolidine-1-carbothioamide

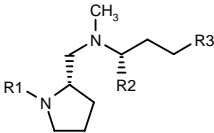


C20 H30 N2 O2 S2; Mol wt: 394.6010

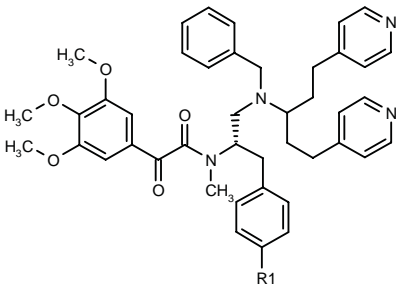
ACTION – Agent with neuronal activity that stimulates nerve growth and prevents neurodegeneration. This compound is metabolically stable, passes through the blood–brain barrier and does not show significant side effects. It is specifically claimed for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, Huntington’s disease, ischemia, stroke, multiple sclerosis, peripheral neuropathy, neuralgia, muscular atrophy and Guillain-Barré syndrome. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
301590	3-Pyr-COCO	H	Ph	C ₂₁ H ₂₄ N ₂ O ₄ S
301592	3,4,5-(MeO)3-PhCOCO	4-Pyr-CH2CH2	4-Pyr	C ₃₁ H ₃₇ N ₃ O ₇ S
301593	COCOC(Me)2Et	3-Pyr-CH2CH2	3-Pyr	C ₂₇ H ₃₇ N ₃ O ₄ S



Compound	R1	R2	R3	Formula
301594	4-Me-PhSO2	H	3-Pyr	C ₂₁ H ₂₉ N ₂ O ₂ S
301595	3,4,5-(MeO)3-PhCOCO	3-Pyr-(CH2)3	CH2Ph	C ₃₅ H ₄₅ N ₃ O ₅



Compound	R1	Formula
301596	H	C ₄₃ H ₄₈ N ₄ O ₅
301597	Cl	C ₄₃ H ₄₇ ClN ₄ O ₅

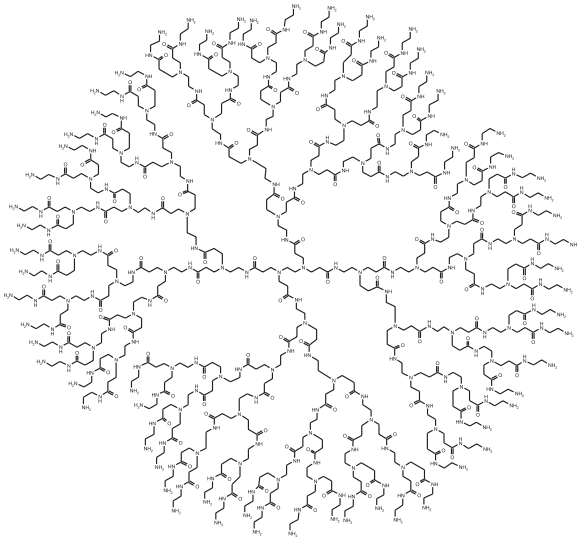
SOURCES – Schering AG; Vertex.

REFERENCES

1. Brumby, T. et al. (Schering AG;Vertex Pharmaceuticals Inc.) *Piperidine and pyrrolidine derivs. displaying neuronal activity*. WO 0112622.

302980

64-Cascade:ethylene-1,2-diamine[*N,N,N',N'*]:(1,4-diaza-5-oxoheptylidene)4:3-aza-4-oxohexylamine



C622 H1248 N250 O124; Mol wt: 14214.3300

ACTION – Branched polyamine proven to eliminate the protease-resistant isoform of the prion protein from scrapie-infected neuroblastoma ScN2a cells in culture. Potentially useful for the treatment of prion disease and a variety of neurodegenerative diseases.

SOURCE – University of California, San Francisco, San Francisco, CA (US).

REFERENCES

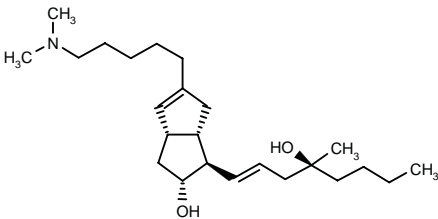
1. Supattapone, S. et al. *Branched polyamines cure prion-infected neuroblastoma cells.* J Virol 2001, 75(7): 3453.

2. Supattapone, S. et al. *Elimination of prions by branched polyamines and implications for therapeutics.* Proc Natl Acad Sci USA 1999, 96(25): 14529.

TREATMENT DISORDERS
OF COGNITION

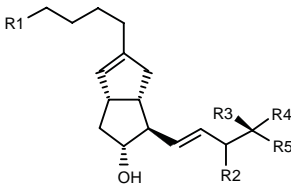
301201

(2*R*,3*R*,3*aS*,6*aS*)-5-[5-(Dimethylamino)pentyl]-3-[4(*S*)-hydroxy-4-methyl-1(*E*)-octenyl]-1,2,3,3*a*,4,6*a*-hexahydro-pentalen-2-ol



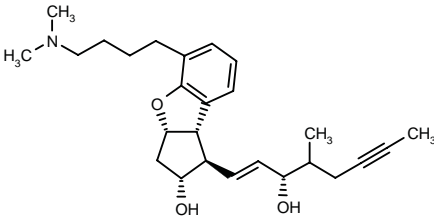
C24 H43 N O2; Mol wt: 377.6087

ACTION – Neurotrophic agent shown to promote neurite outgrowth in murine neuroblastoma Neuro-2A cells, being more potent than PGE₁. It was also found to ameliorate learning and memory impairment induced by i.c.v. infusion of β-amyloid protein(1-42) in the step-through passive avoidance and Y-maze tests in rats. Compound was devoid of hypotensive activity at 0.1-1 mg/kg i.v. in rats and it exhibited good blood–brain barrier permeability, as demonstrated *in vitro* by measuring its uptake into bovine cerebral capillary endothelial cells. Potentially useful for the treatment of neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis, as well as demyelinating diseases, meningitis, Creutzfeldt-Jakob disease, peripheral nerve disorders, cerebrovas-cular disorders, neuropathy and nephropathy, and cerebral tumors. Other exemplified compounds from this series of nitrogen-containing derivatives include the following:

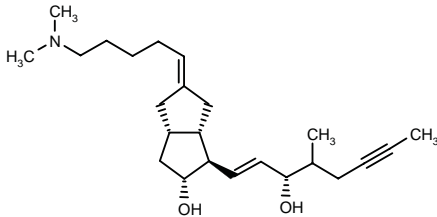


Compound	R1	R2	R3	R4	R5	Formula
301295	CONH2	H	Me	OH	Bu	C ₂₂ H ₃₇ NO ₃
301296	CON(Me)2	H	Me	OH	Bu	C ₂₄ H ₄₁ NO ₃
301298	CH2N(Me)2	H	H	H	3-Me-Ph	C ₂₆ H ₃₉ NO
301300	CH2N(Me)2	(S)-OH	H	H	3-Me-Ph	C ₂₆ H ₃₉ NO ₂

Compound	R1	R2	R3	R4	R5	Formula
301301	4-morpholinyl-CH2	H	H	H	3-Me-Ph	C ₂₈ H ₄₁ NO ₂
301302	CH2N(i-Pr)2	H	H	H	3-Me-Ph	C ₃₀ H ₄₇ NO
301303	1-pyrrolidinyl-CH2	(R)-OH	H	H	3-Me-Ph	C ₂₈ H ₄₁ NO ₂
301304	CON(Me)2	H	H	H	3-Me-Ph	C ₂₆ H ₃₇ NO ₂



301297: C26 H37 N O3



301299: C24 H39 N O2

SOURCE – Teijin.

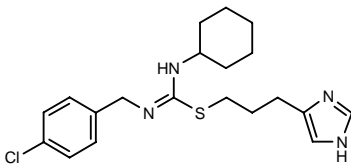
REFERENCES

1. Sugiura, S. et al. (Teijin Ltd.) *Neuropathy improvers containing nitrogenous cpds. as the active ingredient.* WO 0110433.

VUF-5228

303824

*N*³-(4-Chlorobenzyl)-*N*¹-cyclohexyl-*S*-[3-[4(5)-imidazolyl]-propyl]isothiurea



C20 H27 Cl N4 S; Mol wt: 390.9803

ACTION – Histamine H₃ receptor antagonist (pK_i = 9.3) potentially useful for the treatment of neurological disorders such as cognition and memory deficits, obesity, epilepsy and sleeping disorders.

SOURCES – University of Cambridge, Cambridge (GB); De Novo Pharmaceuticals; Vrije Universiteit, Amsterdam (NL).

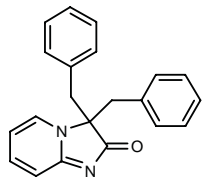
REFERENCES

1. De Esch, I.J.P. et al. *Development of a pharmacophore model for histamine H3 receptor antagonists, using the newly developed molecular modeling program SLATE.* J Med Chem 2001, 44(11): 1666.

ZSET-845

301080

3,3-Dibenzylimidazo[1,2-a]pyridin-2(3*H*)-one



C21 H18 N2 O; Mol wt: 314.3862

ACTION – Cerebral function-improving agent active in a number of preclinical models of memory impairment. Compound was able to inhibit scopolamine-induced amnesia in mice (0.01-10 mg/kg) and to ameliorate performance in the radial maze (0.1 mg/kg), with improved activity compared to tacrine and donepezil. Compound (1-10 mg/kg p.o.) was also seen to ameliorate performance in a model of β -amyloid(25-35)-induced memory impairment in the passive avoidance in rats. Moreover, compound enhanced choline acetyltransferase activity in the basal forebrain, medial septum and hippocampus which was decreased by the administration of β -amyloid (25-35). Potentially useful for the treatment of cognitive deficits such as Alzheimer’s disease.

SOURCE – Zenyaku Kogyo.

REFERENCES

1. Kawashima, S. et al. (Zenyaku Kogyo Co., Ltd.) *Azaindolizone derivs. and cerebral function improvers containing the same as the active ingredient*. WO 0109131.

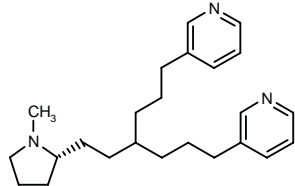
2. Yamaguchi, Y. et al. *Ameliorative effects of ZSET845, a novel cognitive enhancer, on deficits of passive avoidance and radial-arm maze learning in the rat*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst V-AD-29.

3. Yamaguchi, Y. et al. *Antiamnesic effects of azaindolizone derivative ZSET845 on learning impairment and decrease in choline acetyltransferase activity induced by amyloid beta 25-35 in the rat*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst V-AD-30.

TREATMENT OF
CEREBROVASCULAR DISEASES

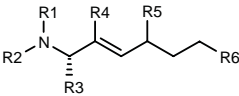
300981

3-[4-[2-[1-Methylpyrrolidin-2(*R*)-yl]ethyl]-7-(3-pyridyl)-heptyl]pyridine

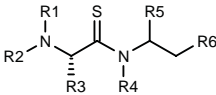


C24 H35 N3; Mol wt: 365.5615

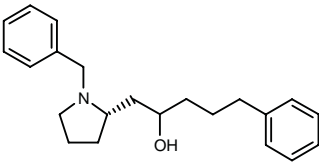
ACTION – Neurotrophic agent with potential for the treatment or prevention of neuronal damage associated with neurological diseases, and particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. Other exemplified compounds from this series of acyclic and cyclic amine derivatives include the following:



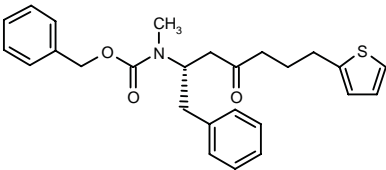
Compound	R1	R2	R3	R4	R5	R6	Formula
300982	Ac		-(CH2)3-	H	3-Pyr- -(CH2)3	3-Pyr- -CH2	C ₂₈ H ₃₃ N ₃ O
300988	Me		-(CH2)3-	F	H	CH2Ph	C ₁₇ H ₂₄ FN
300989	Me	Ac	CH2Ph	F	H	Ph	C ₂₂ H ₂₆ FNO



Compound	R1	R2	R3	R4	R5	R6	Formula
300983	COPh		-(CH2)3-	H	3-Pyr- -(CH2)3	3-Pyr- -(CH2)2	C ₂₉ H ₃₄ N ₄ OS
300984	COCOPh		-(CH2)3-	3-Pyr- -(CH2)2	H	H	C ₂₂ H ₂₈ N ₃ O ₂ S
300985	Me	Et	CH2Ph	Me	H	3-Pyr	C ₂₉ H ₂₇ N ₃ S



300986: C22 H29 N O



300987: C26 H29 N O3 S

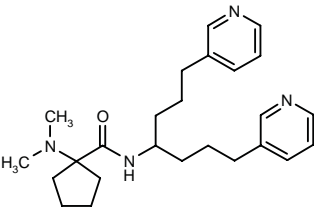
SOURCE – Vertex.

REFERENCES

1. Mullican, M. et al. (Vertex Pharmaceuticals Inc.) *Acyclic and cyclic amine derivs*. WO 0108685.

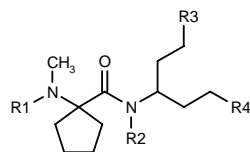
300990

1-(Dimethylamino)-*N*-[4-(3-pyridyl)-1-[3-(3-pyridyl)propyl]-butyl]cyclopentanecarboxamide



C25 H36 N4 O; Mol wt: 408.5864

ACTION – Neurotrophic agent with potential for the treatment or prevention of neuronal damage associated with neurological diseases, and particularly for the treatment of Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, stroke, neuralgias, muscular atrophies and Guillain-Barré syndrome. Other exemplified compounds from this series of cyclic amine derivatives include the following:



Compound	R1	R2	R3=R4	Formula
300991	CH2Ph	H	3-Pyr-CH2	C ₃₁ H ₄₀ N ₄ O
300992	COPh	H	3-Pyr-CH2	C ₃₁ H ₃₈ N ₄ O ₂
300993	COCOPh	H	3-Pyr-CH2	C ₃₂ H ₃₈ N ₄ O ₃
300994	CH2Ph	CH2Ph	4-Pyr	C ₃₆ H ₄₂ N ₄ O
300995	CO2CH2Ph	CH2Ph	4-Pyr	C ₃₇ H ₄₂ N ₄ O ₃
300997	Me	4-Pyr-CH2	CH2Ph	C ₃₃ H ₄₃ N ₃ O
300998	Ac	4-Pyr-CH2	CH2Ph	C ₃₄ H ₄₃ N ₃ O ₂
300999	COCOPh	4-Pyr-CH2	CH2Ph	C ₄₀ H ₄₅ N ₃ O ₃

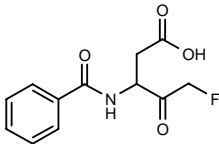
SOURCE – Vertex.

REFERENCES

1. Mullican, M. and Lauffer, D. (Vertex Pharmaceuticals Inc.) *Cyclic amine derivs. for the treatment of neurological diseases.* WO 0109097.

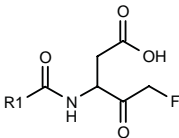
301122

3-Benzamido-5-fluoro-4-oxopentanoic acid



C12 H12 F N O4; Mol wt: 253.2278

ACTION – Inhibitor of caspases that mediate cell apoptosis and inflammation, particularly caspase 8 and caspase 9. This compound was also active in a FAS-induced apoptosis assay with an IC₅₀ < 200 nM. Potentially useful for the treatment of stroke, cerebral and spinal cord injury, meningitis, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, spinal muscular atrophy, myocardial infarction, atherosclerosis, multiple sclerosis and neurodegenerative disorders, among others. Other exemplified compounds are:



Compound	R1	Formula
301123	2-Cl-Ph	C ₁₂ H ₁₁ ClFNO ₄
301124	3,4-(Cl)2-Ph	C ₁₂ H ₁₀ Cl ₂ FNO ₄
301125	3-F-Ph	C ₁₂ H ₁₁ F ₂ NO ₄
301126	4-CF3-Ph	C ₁₃ H ₁₁ F ₄ NO ₄
301129	3-MeO-Ph	C ₁₃ H ₁₄ FNO ₅
301130	3-CN-Ph	C ₁₃ H ₁₁ FN ₂ O ₄
301132	1-Naph	C ₁₆ H ₁₄ FNO ₄
301133	3-Pyr	C ₁₁ H ₁₁ FN ₂ O ₄
301134	2-thienyl	C ₁₀ H ₁₀ FNO ₄ S
301135	2-indolyl	C ₁₄ H ₁₃ FN ₂ O ₄
301136	5-Ph-2-furyl	C ₁₆ H ₁₄ FNO ₅
301137	3-(PhO)-Ph	C ₁₈ H ₁₆ FNO ₅

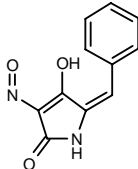
SOURCE – Vertex.

REFERENCES

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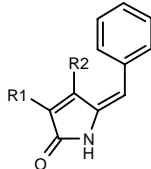
301273

5-Benzylidene-4-hydroxy-3-nitroso-2,5-dihydro-1 H-pyrrol-2-one



C11 H8 N2 O3; Mol wt: 216.1952

ACTION – Glycine-site NMDA receptor antagonist with potential for the treatment or prevention of pain, as well as inflammation, allergy, depression, drug and alcohol abuse, gastritis, diarrhea, urinary incontinence, cardiovascular disorders, respiratory disorders, cough, epilepsy, schizophrenia, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, cerebral ischemia, stroke, hypoxia, anoxia, Tourette’s syndrome and anxiety. Other exemplified compounds from this series of substituted 1,5-dihydropyrrol-2-one derivatives are:



Compound	R1	R2	Formula
301274	NO	OMe	C ₁₂ H ₁₀ N ₂ O ₃
301275	NO	NHCH2Ph	C ₁₈ H ₁₅ N ₃ O ₂
301276	NO	NHPh	C ₁₇ H ₁₃ N ₃ O ₂
301277	NO	NHMe	C ₁₂ H ₁₁ N ₃ O ₂
301278	NO	NH2	C ₁₁ H ₉ N ₃ O ₂
301279	NO2	OH	C ₁₁ H ₈ N ₂ O ₄
301280	NO2	NHPh	C ₁₇ H ₁₃ N ₃ O ₃
301281	NO2	NHCH2Ph	C ₁₈ H ₁₅ N ₃ O ₃
301282	NO2	NHMe	C ₁₂ H ₁₁ N ₃ O ₃
301283	NO2	NH2	C ₁₁ H ₉ N ₃ O ₃

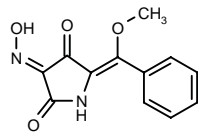
SOURCE – Grünenthal.

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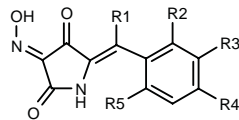
301285

5-(1-Methoxy-1-phenylmethylene)pyrrolidine-2,3,4-trione 3-oxime



C12 H10 N2 O4; Mol wt: 246.2210

ACTION – Glycine-site NMDA receptor antagonist (K_i = 0.116 μ M), with potential for the treatment or prevention of pain, as well as inflammation, allergy, depression, drug and alcohol abuse, gastritis, diarrhea, urinary incontinence, cardiovascular disorders, respiratory disorders, cough, epilepsy, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, cerebral ischemia, stroke, hypoxia, anoxia, Tourette's syndrome and anxiety. Other exemplified compounds from this series of substituted pyrrolidin-2,3,4-trione-3-oxime derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
301286	Br	H	H	H	H	C ₁₁ H ₇ BrN ₂ O ₃
301287	H	H	H	H	H	C ₁₁ H ₈ N ₂ O ₃
301288	H	H	H	H	Cl	C ₁₁ H ₇ ClN ₂ O ₃
301289	H	H	H	Cl	H	C ₁₁ H ₇ ClN ₂ O ₃
301290	H	Cl	Cl	H	H	C ₁₁ H ₆ Cl ₂ N ₂ O ₃
301292	H	H	H	Cl	Cl	C ₁₁ H ₆ Cl ₂ N ₂ O ₃
301293	H	Cl	H	H	Cl	C ₁₁ H ₆ Cl ₂ N ₂ O ₃
301294	H	H	Cl	H	H	C ₁₁ H ₇ ClN ₂ O ₃

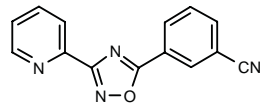
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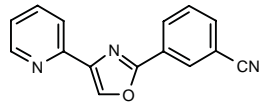
301541

3-[3-(2-Pyridyl)-1,2,4-oxadiazol-5-yl]benzonitrile



C14 H8 N4 O; Mol wt: 248.2442

ACTION – Metabotropic glutamate mglu₅ receptor antagonist that exhibited IC₅₀ values of 45 and 74 nM when tested using a chimeric CaR/mglu_{5d} receptor and the native mglu_{5d} receptor, respectively. It is expected to be useful for the treatment of neurological and psychiatric disorders such as stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, epilepsy, pain, migraine, Parkinson's disease, senile dementia, Huntington's chorea and Alzheimer's disease. Another exemplified heterocyclic compound is:



301542: C15 H9 N3 O

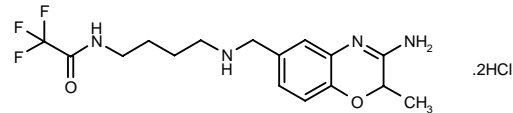
SOURCE – NPS Pharmaceuticals.

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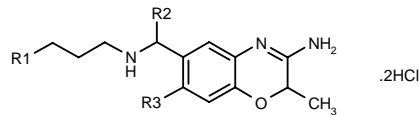
301828

N-[4-(3-Amino-2-methyl-2H-1,4-benzoxazin-6-ylmethyl-amino)butyl]-2,2,2-trifluoroacetamide dihydrochloride



C16 H21 F3 N4 O2 . 2HCl; Mol wt: 431.2837

ACTION – Agent for the treatment of neurodegenerative, inflammatory, autoimmune and cardiovascular disorders, an inhibitor of nitric oxide synthase (NOS), particularly neuronal NOS. Other specifically claimed compounds from this series of benzoxazine and benzothiazine derivatives are:



Compound	R1	R2	R3	Formula
301829	CH2NHCSCF3	H	H	C ₁₆ H ₂₁ F ₃ N ₄ O ₂ .2HCl
301830	4-Cl-PhCONHCH2	H	H	C ₂₁ H ₂₅ ClN ₄ O ₂ .2HCl
301831	4-Cl-PhCSNHCH2	H	H	C ₂₁ H ₂₅ ClN ₄ O ₂ .2HCl
301832	CH2NHCOPh	H	H	C ₂₁ H ₂₆ N ₄ O ₂ .2HCl
301833	CH2CH2NHCOCF3	H	H	C ₁₇ H ₂₃ F ₃ N ₄ O ₂ .2HCl
301834	4-Cl-PhCONHCH2CH2	H	H	C ₂₂ H ₂₇ ClN ₄ O ₂ .2HCl
301835	CH2NHCONHPh	H	H	C ₂₁ H ₂₇ N ₅ O ₂ .2HCl
301836	2-thioxo-1-pyrrolidinyl	H	H	C ₁₇ H ₂₄ N ₄ O ₂ .2HCl
301837	CH2NHCOCF3	-(CH2)3-		C ₁₉ H ₂₅ F ₃ N ₄ O ₂ .2HCl
301838	CH2CH2NHCO2Me	H	H	C ₁₆ H ₂₆ N ₄ O ₃ .2HCl

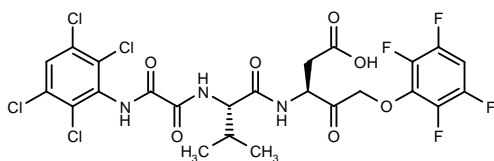
SOURCE – Schering AG.

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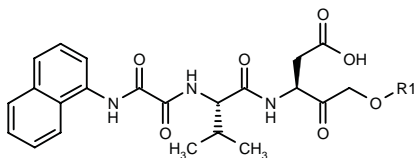
304484

3(S)-[N-[2-(2,3,5,6-Tetrachlorophenylamino)-2-oxoacetyl]-L-valylamino]-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid



C24 H19 Cl4 F4 N3 O7; Mol wt: 679.2321

ACTION – Broad-spectrum caspase inhibitor with nanomolar activity against caspase 2, caspase 3, caspase 4 and caspase 8 (K_i = 3.7, 36.1, 31.1 and 4.0 nM, respectively). Compound also showed excellent cellular activity in models of apoptosis including Jurkat Z6-1 cells and human SKW 6.4 B-cells exposed to anti-fas CH11 (IC_{50} = 0.22 and 0.41 μ M, respectively), human monocytic THT-1 cells stimulated with lipopolysaccharide (LPS; IC_{50} = 1.05 μ M) and rats embryonic cortical neurons exposed to concanavalin A (IC_{50} = 0.66 μ M). *In vivo*, in a model of middle cerebral artery occlusion in rats, compound at a dose of 30 mg/kg i.v. given 1 h after insult produced an 18% reduction in infarct size. Potentially useful for the treatment of stroke. Within this series of oxamyl dipeptides, the following are also included:



Compound	R1	Formula
302049	2,3,5,6-(F)4-Ph	$C_{28}H_{26}F_4N_3O_7$
302050	2,4,6-(F)3-Ph	$C_{28}H_{26}F_3N_3O_7$
302051	2,6-(Cl)2-PhCO	$C_{29}H_{27}Cl_2N_3O_8$
302052	PO(Ph)2	$C_{34}H_{34}N_3O_8P$

SOURCES – Idun Pharmaceuticals; Novartis.

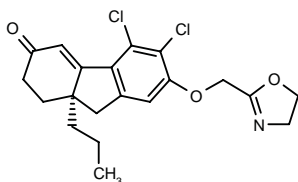
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GERI-E7

301690

(+)-(9a*R*)-5,6-Dichloro-7-(4,5-dihydrooxazol-2-yl-methoxy)-9a-propyl-2,3,9,9a-tetrahydro-1*H*-fluoren-3-one



C20 H21 Cl2 N O3; Mol wt: 394.2959

ACTION – Neuroprotective agent, a representative compound from a series of fluorenone derivatives that potently inhibit the unwanted release of excitotoxins by astrocyte cells following an injury or insult to the brain or spinal cord and are further reported to be able to reduce swelling in astrocyte cells, thereby helping promote proper blood flow through the brain following head injury or other crises. *In vitro*, compound gave an IC_{50} value of 8.5 μ M for inhibition of D-aspartate release by osmotically stressed human astrocytoma UC11-MG cells, being more potent than reference compound L-644711 (IC_{50} = 263.5 μ M). *In vivo*, it was shown to be effective in a global brain ischemia model in gerbils and in a focal brain ischemia model in rats at 20 mg/kg i.v.

SOURCE – Questcor.

REFERENCES

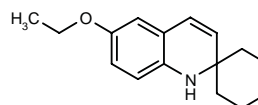
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S-33113*

288792

6'-Ethoxyspiro[cyclohexane-1,2'-(1'*H*)-quinoline]

S-33113-1



C16 H21 N O ; Mol wt: 279.8088

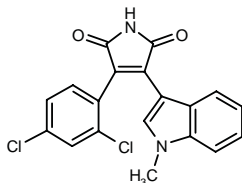
ACTION – Neuroprotective agent with *in vitro* antioxidant activity in mouse cortical membranes (IC_{50} = 0.29 μ M for inhibition of Fenton reaction-induced lipid peroxidation) and *in vivo* neuroprotective activity in several models of cerebral degeneration. Compound showed no affinity for 28 different receptors and uptake systems and showed negligible inhibition of COX-1 (> 10 μ M), with a slight inhibition of COX-2 and 5-lipoxygenase (~ 10 μ M). In rats, compound (150 mg/kg i.p. or 600 mg/kg p.o.) markedly reduced lethality induced by *t*-butylhydroperoxide and significantly attenuated alloxan-mediated hyperglycemia at 400 and 600 mg/kg p.o. Moreover, compound prevented hippocampal cell death induced by either transient global ischemia or kainic acid when given before injury at a dose of 150 mg/kg i.p. Furthermore, it significantly prevented D-methamphetamine-mediated dopamine depletion in mice striatum at a dose of 150 mg/kg i.p. or p.o.

SOURCE – Servier.

REFERENCES

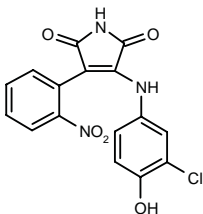
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*Identified compound **288792** Drug Data Rep 2000, 022(08): 0687.

SB-216763^{1,3,4}**300887**3-(2,4-Dichlorophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione

C19 H12 Cl2 N2 O2; Mol wt: 371.2218

ACTION – Potent and selective cell-permeable inhibitor of glycogen synthase kinase-3 (GSK3; $K_i = 9$ nM) proven able to stimulate glycogen synthesis in human liver cells and to induce expression of a β -catenin-LEFT/TCF-regulated reporter gene in HEK293 cells. In addition, compound protected cerebellar granule neurons or dorsal root growth neurons following survival factor withdrawal or inhibition of PI-3 kinases. Potentially useful for the treatment of type 2 diabetes and neurodegenerative diseases. Another related compound is:

**SB-415286 [300888]:²⁻⁵** C16 H12 Cl N3 O5**SOURCE** – GlaxoSmithKline.**REFERENCES**

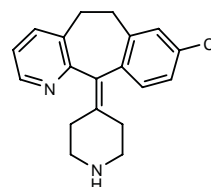
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RESPIRATORY DRUGS**TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS****DESLO RATADINE**

Prop INN, USAN

1099088-Chloro-6,11-dihydro-11-(4-piperidylidene)-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridine

Descarboethoxyloratadine
Sch-34117⁺
ClarinetTM
Opulis



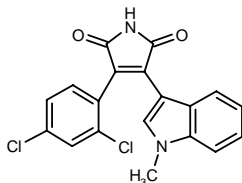
C19 H19 Cl N2; Mol wt: 310.8261

ACTION – Selective histamine H_1 receptor antagonist.**INDICATION** – Treatment of seasonal allergic rhinitis.**PRESENTATION** – Film-coated tablets, 5 mg.**PROPRIETARY NAMES** – *Aerius* (DE); *NeoClarityn* (GB).**SOURCES** – Sepracor; marketed by Schering-Plough.**RECENT REFERENCES**

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- Baena-Cagnani, C. *Desloratadine improved asthma symptoms and decreased β_2 -agonist use in patients with seasonal allergic rhinitis and concomitant asthma*. Allergy 2001, 56(Suppl. 68): Abstr 60.
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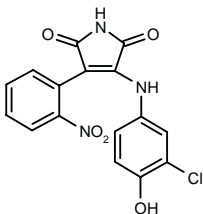
SB-216763^{1,3,4}**300887**

3-(2,4-Dichlorophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione



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SB-415286 [300888]:²⁻⁵ C16 H12 Cl N3 O5

SOURCE – GlaxoSmithKline.

REFERENCES

1. Coghlan, M.P. et al. (SmithKline Beecham plc) *Treatment of conditions with a need for the inhibition of GSK-3*. WO 0038675.
2. Coghlan, M.P. et al. (SmithKline Beecham plc.) *Novel method and cpds*. WO 0021927.
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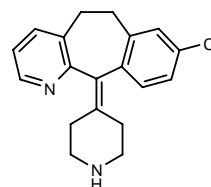
RESPIRATORY DRUGS**TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS****DESLO RATADINE**

Prop INN, USAN

109908

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridine

Descarboethoxyloratadine
Sch-34117⁺
ClarinetTM
Opulis



C19 H19 Cl N2; Mol wt: 310.8261

ACTION – Selective histamine H_1 receptor antagonist.

INDICATION – Treatment of seasonal allergic rhinitis.

PRESENTATION – Film-coated tablets, 5 mg.

PROPRIETARY NAMES – *Aerius* (DE); *NeoClarityn* (GB).

SOURCES – Sepracor; marketed by Schering-Plough.

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2. Afrime, M.B. et al. *Lack of electrocardiographic effects when desloratadine and ketoconazole are coadministered*. Allergy 2000, 55(Suppl. 63): Abst 992.
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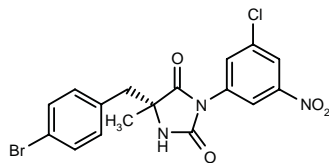
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*Drug Data Reo 1997, 009(08): 0670.

ASTHMA THERAPY

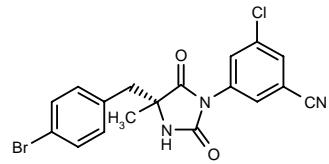
300608

5(R)-(4-Bromobenzyl)-3-(3-chloro-5-nitrophenyl)-5-methylimidazolidine-2,4-dione



C17 H13 Br Cl N3 O4; Mol wt: 438.6637

ACTION – Agent for the treatment or prevention of inflammatory and immune-mediated diseases, particularly asthma, which acts by antagonizing the binding of human intercellular adhesion molecules such as ICAM-1, ICAM-2 and ICAM-3 to leukointegrins, especially CD18/CD11a (also known as LFA-1). Another specifically claimed compound is:



300609: C18 H13 Br Cl N3 O2

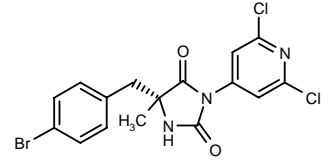
SOURCE – Boehringer Ingelheim.

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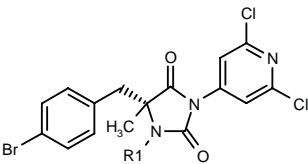
300610

5(R)-(4-Bromobenzyl)-3-(2,6-dichloropyridin-4-yl)-5-methylimidazolidine-2,4-dione



C16 H12 Br Cl2 N3 O2; Mol wt: 429.0998

ACTION – Agent for the treatment or prevention of inflammatory and immune-mediated diseases, particularly asthma, which acts by antagonizing the binding of human intercellular adhesion molecules such as ICAM-1, ICAM-2 and ICAM-3 to leukointegrins, especially CD18/CD11a (also known as LFA-1). Other specifically claimed compounds are:



Compound	R1	Formula
300771	Et	C ₁₈ H ₁₆ BrCl ₂ N ₃ O ₂
300772	Ac	C ₁₈ H ₁₄ BrCl ₂ N ₃ O ₃

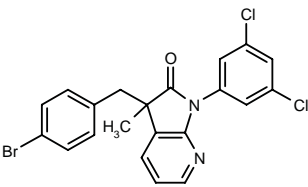
SOURCE – Boehringer Ingelheim.

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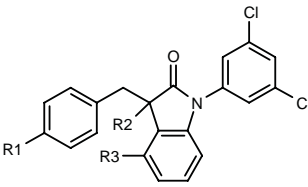
300611

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-2-one



C21 H15 Br Cl2 N2 O; Mol wt: 462.1725

ACTION – Agent for the treatment or prevention of inflammatory and immune-mediated diseases, particularly asthma, which acts by antagonizing the binding of human intercellular adhesion molecules such as ICAM-1, ICAM-2 and ICAM-3 to leukointegrins, especially CD18/CD11a (also known as LFA-1). *In vitro*, compound inhibited the binding of human LFA-1 to sICAM-1 with a K_d value of 0.375 μM. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
300612	H	Me	H	C ₂₂ H ₁₇ Cl ₂ NO
300613	H	H	OMe	C ₂₂ H ₁₇ Cl ₂ NO ₂
300614	Br	H	OH	C ₂₁ H ₁₄ BrCl ₂ NO ₂

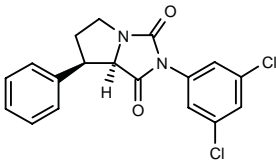
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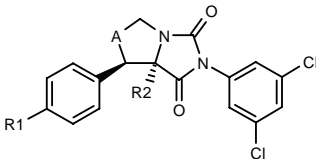
300615

(7*R**,7*aR**)-2-(3,5-Dichlorophenyl)-7-phenylperhydro-pyrrolo[1,2-*c*]imidazole-1,3-dione



C18 H14 Cl2 N2 O2; Mol wt: 361.2266

ACTION – Agent for the treatment or prevention of inflammatory and immune-mediated diseases, particularly asthma, which acts by antagonizing the binding of human intercellular adhesion molecules such as ICAM-1, ICAM-2 and ICAM-3 to leukointegrins, especially CD18/CD11a (also known as LFA-1). Other specifically claimed compounds include the following:



Compound	R1	R2	A	Formula
300616	H	Me	-CH2-	C ₁₉ H ₁₆ Cl ₂ N ₂ O ₂
300617	Br	H	-CH2-	C ₁₈ H ₁₃ BrCl ₂ N ₂ O ₂
300618	H	Me	-(CH2)2-	C ₂₀ H ₁₈ Cl ₂ N ₂ O ₂
300619	H	OMe	-(CH2)2-	C ₂₀ H ₁₈ Cl ₂ N ₂ O ₃

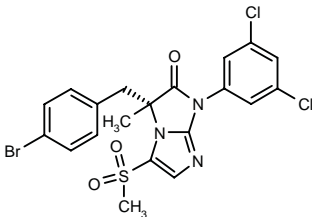
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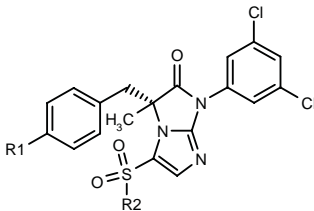
300620

3(*R*)--(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-5-(methylsulfonyl)-2,3-dihydro-1*H*-imidazo[1,2-*a*]imidazol-2-one



C20 H16 Br Cl2 N3 O3 S; Mol wt: 529.2404

ACTION – Agent for the treatment or prevention of inflammatory and immune-mediated diseases, particularly asthma, which acts by antagonizing the binding of human intercellular adhesion molecules such as ICAM-1, ICAM-2 and ICAM-3 to leukointegrins, especially CD18/CD11a (also known as LFA-1). Other specifically claimed compounds from this series of imidazoimidazoles and triazoles include the following:



Compound	R1	R2	Formula
300621	5-pyrimidinyl	-L-Pro-OH	C ₂₈ H ₂₄ Cl ₂ N ₆ O ₅ S
300622	5-pyrimidinyl	4-(NH2CO)-1-Pip	C ₂₉ H ₂₇ Cl ₂ N ₇ O ₄ S
300623	5-pyrimidinyl	1-Piz	C ₂₇ H ₂₅ Cl ₂ N ₇ O ₃ S
300624	CN	4-Ac-1-Piz	C ₂₆ H ₂₄ Cl ₂ N ₆ O ₄ S
300625	CN	4-(MeNHCO)-1-Piz	C ₂₆ H ₂₅ Cl ₂ N ₇ O ₄ S

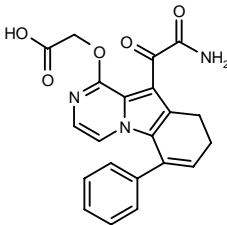
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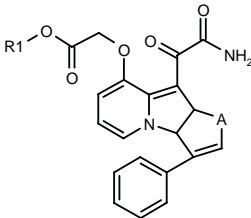
300634

2-[10-(2-Amino-2-oxoacetyl)-6-phenyl-8,9-dihydro-pyrazino[1,2-*a*]indol-1-yloxy]acetic acid

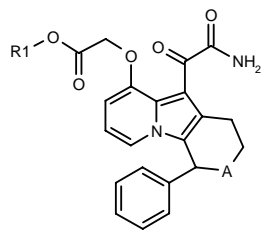


C21 H17 N3 O5; Mol wt: 391.3813

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 0.034 μM against human enzyme) for use in the treatment of a broad range of disorders including septic shock, adult respiratory distress syndrome, pancreatitis, bronchial asthma, allergic rhinitis, rheumatoid arthritis, arteriosclerosis, cerebral hemorrhage, cerebral infarction, inflammatory bowel disease, psoriasis, heart failure and myocardial infarction. Other exemplified compounds from this series of tricyclic derivatives include the following:



Compound	R1	A	Formula
300636	Me	-(CH2)2-	C ₂₃ H ₂₀ N ₂ O ₅
300637	H	-(CH2)2-	C ₂₂ H ₁₈ N ₂ O ₅
300643	Me	S	C ₂₁ H ₁₆ N ₂ O ₅ S
300645	H	S	C ₂₀ H ₁₄ N ₂ O ₅ S



Compound	R1	A	Formula
300638	Me	CH2	C ₂₃ H ₂₂ N ₂ O ₅
300639	H	CH2	C ₂₂ H ₂₀ N ₂ O ₅
300640	H	-N(Ac)-	C ₂₃ H ₂₁ N ₃ O ₆
300641	H	-N(COCF3)-	C ₂₃ H ₁₈ F ₃ N ₃ O ₆

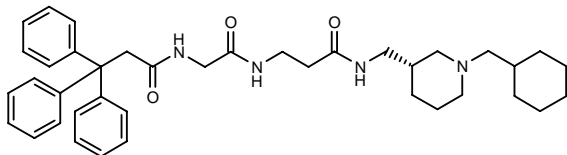
SOURCE – Shionogi.

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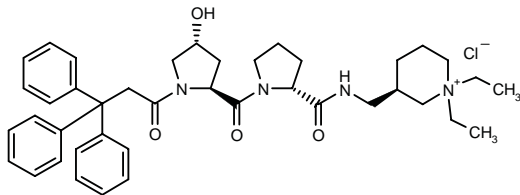
300770

N-[*N*-[3-[1-(Cyclohexylmethyl)piperidin-3(*R*)-ylmethylamino]-3-oxopropyl]carbamoylmethyl]-3,3,3-triphenylpropionamide



C39 H50 N4 O3; Mol wt: 622.8490

ACTION – Selective antagonist of the muscarinic M₃ receptor with high potency and selectivity relative to M₁ and M₂ receptors in binding and functional assays. This compound potently inhibited acetylcholine-induced bronchoconstriction in rats (ED₅₀ = 15 µg/kg i.v.). It is potentially useful for the treatment of respiratory, urologic and digestive diseases including asthma, chronic bronchitis, pulmonary emphysema, irritable bowel syndrome, gastroduodenal ulcer and urinary incontinence among others. Another exemplified compound is:



300773: C41 H53 Cl N4 O4

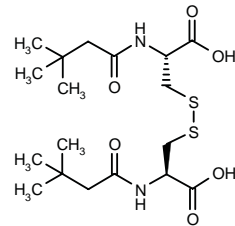
SOURCE – Banyu.

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300819

N,N'-Bis(3,3-dimethylbutyryl)-L-cystine



C18 H32 N2 O6 S2; Mol wt: 436.5908

ACTION – Agent for the treatment or prevention of inflammatory, allergic and immune diseases caused by leukocyte infiltration that inhibits cell adhesion mediated by adhesion molecules, in particular VLA-4. *In vitro*, compound inhibited the binding of the CS-1 peptide to VLA-4 with an IC₅₀ value of 1800 nM. *In vivo*, it was shown to inhibit pollen-induced peritonitis in mice (31.1% inhibition at 400 mg/kg i.v.), as well as 2,4-dinitro-fluorobenzene-induced ear edema in mice (40.3% inhibition at 400 mg/kg i.v. + 0.3 mg/ear topically). In addition, it inhibited ovalbumin-induced eosinophil infiltration into the bronchoalveolar lavage (BAL) of sensitized mice following intranasal administration and was effective in an antigen-induced guinea pig rhinitis model.

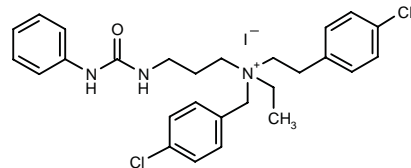
SOURCE – Toray.

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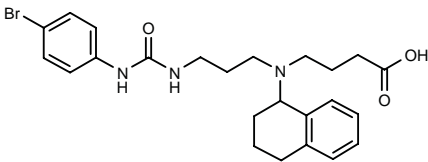
300886

N-(4-Chlorobenzyl)-*N*-[2-(4-chlorophenyl)ethyl]-*N*-ethyl-3-(3-phenylureido)propan-1-aminium iodide



C27 H32 Cl2 I N3 OI; Mol wt: 612.3758

ACTION – Chemokine CCR3 receptor inhibitor with potential in the treatment of CCR3-mediated diseases such as asthma, rhinitis, eczema, inflammatory bowel disease, parasitic infections, autoimmune diseases and HIV infection. *In vitro*, compound gave 100% inhibition of the eotaxin-induced chemotaxis of U-937 cells expressing the CCR3 receptor at 10 µM. *In vivo*, it markedly inhibited collagen-induced arthritis in mice at 50 mg/kg s.c. and was shown to inhibit acetylcholine-induced bronchoconstriction and eosinophil infiltration into bronchoalveolar lavage fluid (BALF) in sensitized mice at 50 mg/kg i.p. Another compound from this series of urea and thiourea derivatives is:



300889: C24 H30 Br N3 O3

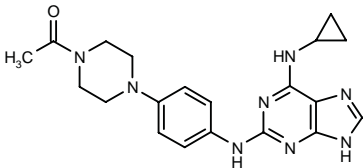
SOURCE – Kirin Brewery.

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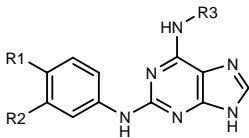
301064

*N*²-[4-(4-Acetylpiperazin-1-yl)phenyl]-*N*⁶-cyclopropyl-9*H*-purine-2,6-diamine



C20 H24 N8 O; Mol wt: 392.4646

ACTION – Inhibitor of syk kinase (IC₅₀ = 2 nM) that also suppresses the IgE-mediated degranulation of mast cells and is thus useful for the treatment of inflammatory or allergic conditions, particularly inflammatory or obstructive airways diseases such as asthma, adult respiratory distress syndrome, chronic obstructive pulmonary or airways disease and bronchitis. Other exemplified purine derivatives are:



Compound	R1	R2	R3	Formula
301065	-NHN=CH-		cyclopropyl	C ₁₅ H ₁₄ N ₈
301066	-CH=NNH-		cyclopropyl	C ₁₅ H ₁₄ N ₈
301067	t-BuOCONH	H	cyclopropyl	C ₁₉ H ₂₃ N ₇ O ₂
301068	-CH=NNH-		Et	C ₁₄ H ₁₄ N ₈
301069	4-morpholinyl	H	cyclopropyl	C ₁₈ H ₂₁ N ₇ O
301070	N(Me)Ac	H	cyclobutyl	C ₁₈ H ₂₁ N ₇ O
301071	-CH=NNH-		cyclobutyl	C ₁₆ H ₁₆ N ₈
301072	4-Me-1-Piz	H	cyclopropyl	C ₁₉ H ₂₄ N ₈
301073	4-Ac-1-Piz	H	cyclobutyl	C ₂₁ H ₂₆ N ₈ O
301074	N(Me)Ac	H	t-Bu	C ₁₈ H ₂₃ N ₇ O
301075	-N=CHCH=CH-		6-indazolyl	C ₂₁ H ₁₅ N ₉
301076	N(Et)Ac	H	i-Pr	C ₁₈ H ₂₁ N ₇ O
301077	N(Me)COEt	H	cyclopropyl	C ₁₈ H ₂₁ N ₇ O
301078	SO ₂ N(Me) ₂	H	i-Pr	C ₁₆ H ₂₁ N ₇ O ₂ S
301079	-CH ₂ OCO-		t-Bu	C ₁₇ H ₁₈ N ₆ O ₂

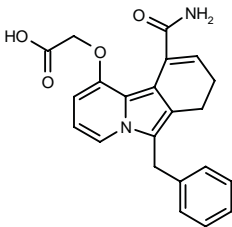
SOURCE – Novartis.

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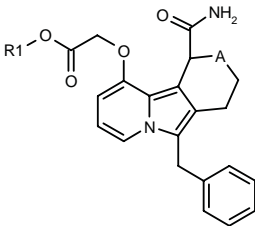
301084

2-(6-Benzyl-10-carbamoyl-7,8-dihydropyrido[2,1-*a*]-isoindol-1-yloxy)acetic acid

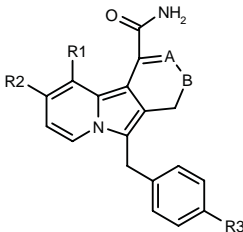


C22 H20 N2 O4; Mol wt: 376.4100

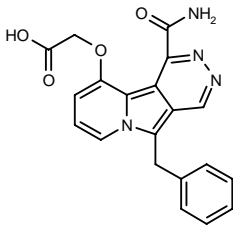
ACTION – Human secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 0.008 μM), potentially useful for the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, bronchial asthma, allergic rhinitis, rheumatoid arthritis, arteriosclerosis, stroke, cerebral infarction, inflammatory bowel disease, psoriasis, heart failure and myocardial infarction. Other exemplified tricyclic compounds are:



Compound	R1	A	Formula
301085	H	-CH ₂ -	C ₂₂ H ₂₂ N ₂ O ₄
301088	Me	-OCH ₂ -	C ₂₃ H ₂₄ N ₂ O ₅
301089	H	-OCH ₂ -	C ₂₂ H ₂₂ N ₂ O ₅
301096	Me	-O-	C ₂₂ H ₂₂ N ₂ O ₅
301097	H	-O-	C ₂₁ H ₂₀ N ₂ O ₅



Compound	R1	R2	R3	A	B	Formula
301086	H	O(CH ₂) ₃ CO ₂ Et	H	CH	CH ₂	C ₂₆ H ₂₈ N ₂ O ₄
301087	H	O(CH ₂) ₃ CO ₂ H	H	CH	CH ₂	C ₂₄ H ₂₄ N ₂ O ₄
301090	OCH ₂ CO ₂ Me	H	H	N	CH ₂	C ₂₂ H ₂₁ N ₃ O ₄
301091	OCH ₂ CO ₂ H	H	H	N	CH ₂	C ₂₁ H ₁₉ N ₃ O ₄
301093	OCH ₂ CO ₂ H	H	H	N	O	C ₂₀ H ₁₇ N ₃ O ₅
301094	OCH ₂ CO ₂ Me	H	Ph	CH	CH ₂	C ₂₉ H ₂₆ N ₂ O ₄
301095	OCH ₂ CO ₂ H	H	Ph	CH	CH ₂	C ₂₈ H ₂₄ N ₂ O ₄



301092: C20 H16 N4 O4

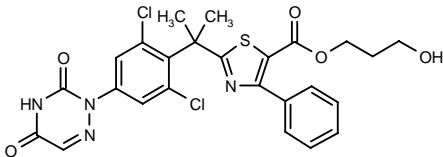
SOURCE – Shionogi.

REFERENCES

1. Ohtani, M. et al. (Shionogi & Co. Ltd.) *Tricyclic cpds. having sPLA2-inhibitory activities*. WO 0109130.

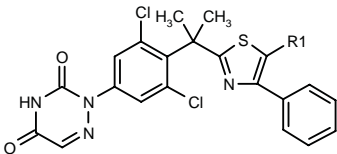
301116

2-[1-[2,6-Dichloro-4-(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)phenyl]-1-methylethyl]-4-phenylthiazole-5-carboxylic acid 3-hydroxypropyl ester



C25 H22 Cl2 N4 O5 S; Mol wt: 561.4438

ACTION – Interleukin-5 (IL-5) inhibitor, potentially useful for the treatment of eosinophil-dependent inflammatory diseases, particularly bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis, and preferably for administration via inhalation. Other specifically claimed 6-azauracil derivatives are:



Compound	R1	Formula
301117	4,4-(Me)2-2-oxo-3-THF-OCO	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₆ S
301118	4-(1-pyrrolidinyl-SO2)-1-Piz-CH2CH2OCO	C ₃₂ H ₃₅ Cl ₂ N ₇ O ₆ S ₂
301121	4,4-(Me)2-2-oxo-3-THF-OCOC(Me)2	C ₃₁ H ₃₀ Cl ₂ N ₄ O ₆ S

SOURCE – Janssen.

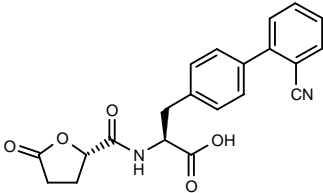
REFERENCES

1. Lacrampe, J.F.A. et al. (Janssen Pharmaceutica NV) *Interleukin-5 inhibiting 6-azauracil derivs*. WO 0110866.

301375

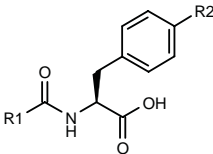
3-(2'-Cyanobiphenyl-4-yl)-2(S)-[5-oxotetrahydrofuran-2(S)-ylcarboxamido]propionic acid

4-(2-Cyanophenyl)-N-[5-oxotetrahydrofuran-2(S)-yl-carbonyl]-L-phenylalanine

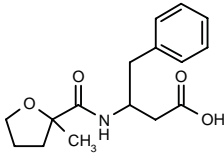


C21 H18 N2 O5; Mol wt: 378.3822

ACTION – Cell adhesion inhibitor, an antagonist of VLA-4 and/or α_4/β_7 and/or $\alpha_9\beta_1$ integrins. Potentially useful in the treatment of pathological conditions characterized by cell adhesion and activation such as asthma, allergic rhinitis, multiple sclerosis, rheumatoid arthritis, inflammation, inflammatory bowel disease, cancer, psoriasis and transplant rejection. Other exemplified compounds from this series of heterocyclic amides include the following:



Compound	R1	R2	Formula
301376	2-(4-Me-2-thiazolyl)-2-THF	2,6-(MeO)2-Ph	C ₂₆ H ₂₈ N ₂ O ₆ S
301377	2-Me-4-(1-pyrrolidinyl)-2-THF	2,6-(MeO)2-4-(1-pyrrolidinyl-CH2)-Ph	C ₃₂ H ₄₃ N ₃ O ₆
301379	3-THF	2-CN-Ph	C ₂₁ H ₂₀ N ₂ O ₄
301380	2-Me-2-THF	F	C ₁₅ H ₁₈ FNO ₄
301381	2-THP	2-MeO-Ph	C ₂₂ H ₂₈ NO ₅
301382	1,1-dioxo-5-Me-tetrahydro-2-thienyl	2-CN-Ph	C ₂₂ H ₂₂ N ₂ O ₅ S
301385	2-Me-2-THF	2,4-(MeO)2-5-pyrimidinyl	C ₂₁ H ₂₈ N ₃ O ₆



301384: C16 H21 N O4

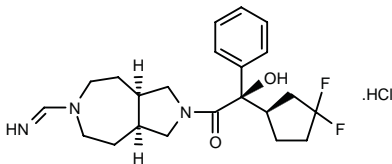
SOURCE – Merck & Co.

REFERENCES

1. Hagmann, W.K. et al. (Merck & Co., Inc.) *Heterocycle amides as cell adhesion inhibitors*. WO 0112183.

301488

2-(*R*)-[3,3-Difluorocyclopent-1(*R*)-yl]-2-hydroxy-1-[(3*aR*,8*aS*)-6-(iminomethyl)perhydropyrrolo[3,4-*d*]azepin-2-yl]-2-phenylethan-1-one hydrochloride



C22 H29 F2 N3 O2 . HCl; Mol wt: 441.9470

ACTION – A representative compound from a series of *N*-acyl cyclic amine derivatives with selective muscarinic M₃ receptor-antagonist activity, as demonstrated in binding studies (*K*_i = 0.8 and 37.4 nM, respectively, for M₃ and M₂ receptors; ratio M₂/M₃ = 46) and in functional assays measuring the inhibition of carbachol-induced contractions (*K*_B = 0.5 nM in rat trachea [M₃] vs. 80 nM in rat right atrium [M₂]; ratio M₂/M₃ = 160). *In vivo*, compound inhibited methacholine-induced bronchoconstriction in dogs and rats, with a long duration of action. Potentially useful for the treatment of respiratory diseases including asthma, chronic bronchitis, pulmonary emphysema, chronic obstructive pulmonary disease and rhinitis, among others.

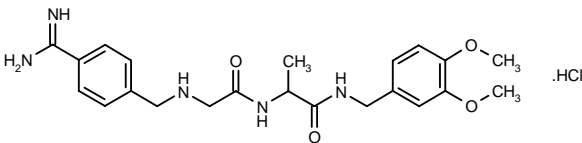
SOURCE – Banyu.

REFERENCES

1. Tsuchiya, Y. et al. (Banyu Pharmaceutical Co., Ltd.) *N-Acyl cyclic amine derivs.* JP 2001039950.

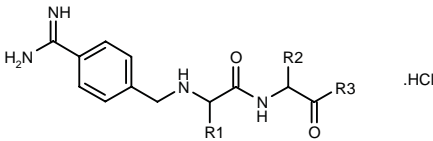
301695

2-[2-(4-Amidinobenzylamino)acetamido]-*N*-(3,4-dimethoxybenzyl)propionamide hydrochloride



C22 H29 N5 O4 . HCl; Mol wt: 463.9630

ACTION – Potent tryptase inhibitor (IC₅₀ < 90 nM against human recombinant enzyme) with high selectivity over factor Xa (IC₅₀ > 110 μM). Claimed for the treatment or prevention of asthma, allergic rhinitis, chronic obstructive pulmonary disease, emphysema, viral and bacterial pulmonary infections and inflammatory responses, rheumatoid arthritis, osteoarthritis, multiple sclerosis, dermatological diseases, psoriasis, conjunctivitis, inflammatory bowel disease, peptic ulcers, cardiovascular diseases, anaphylaxis and cancer. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
301697	4-(CO2Me)-Ph	i-Pr	3-indolyl-CH2CH2NH	C ₃₂ H ₃₆ N ₆ O ₄ .HCl
301699	Me	H	2-Pyr-CH2CH2NH	C ₂₀ H ₂₆ N ₆ O ₂ .HCl
301700	CH2OH	H	2-Pyr-CH2CH2NH	C ₂₀ H ₂₆ N ₆ O ₃ .HCl
301701	H	H	4-(1,3-benzodioxol-5-yl-CH2)-1-Piz	C ₂₄ H ₃₀ N ₆ O ₄ .HCl

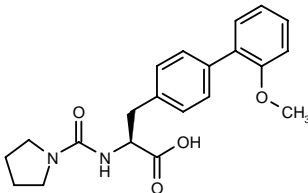
SOURCE – Morphochem.

REFERENCES

1. Weber, L. et al. (Morphochem AG) *Cpds. that inhibit tryptase activity.* DE 19939910, WO 0114320.

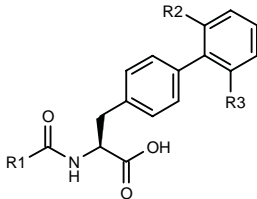
301723

4-(2-Methoxyphenyl)-*N*-(pyrrolidin-1-ylcarbonyl)-L-phenylalanine



C21 H24 N2 O4; Mol wt: 368.4306

ACTION – VLA-4 and/or α₄β₇ and/or α₉β₁ integrin antagonist, potentially useful for the treatment of diseases characterized by cell adhesion and activation such as asthma, allergic rhinitis, allergic conjunctivitis, multiple sclerosis, inflammatory lung diseases, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, restenosis, atherosclerosis, cancer, psoriasis, hepatitis and transplant rejection. Other exemplified compounds from this series of substituted ureas include the following:



Compound	R1	R2	R3	Formula
301725	2-(CO2Me)-1-pyrrolidinyl	H	OMe	C ₂₃ H ₂₆ N ₂ O ₆
301726	6,7-(MeO)2-1,2,3,4-tetrahydro-2-isoquinolinyl	H	CN	C ₂₆ H ₂₇ N ₃ O ₅
301727	4-(CO2Et)-1-Pip	CN	H	C ₂₅ H ₂₇ N ₃ O ₅
301728	4-morpholinyl	H	OMe	C ₂₁ H ₂₄ N ₂ O ₅
301729	cyclohexyl-NH	OMe	OMe	C ₂₄ H ₃₀ N ₂ O ₅
301730	4-morpholinyl	OMe	OMe	C ₂₂ H ₂₆ N ₂ O ₆
301731	3-(CO2Et)-1-Pip	OMe	OMe	C ₂₆ H ₃₂ N ₂ O ₇
301732	N(Me)C6H13	OMe	OMe	C ₂₅ H ₃₄ N ₂ O ₅
301733	N(Me)Ph	OMe	OMe	C ₂₅ H ₂₆ N ₂ O ₅

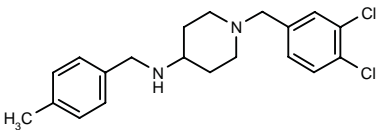
SOURCE – Merck & Co.

REFERENCES

1. Delaszlo, S.E. et al. (Merck & Co., Inc.) *Substd. ureas as cell adhesion inhibitors*. WO 0114328.

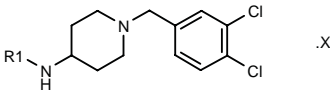
301809

1-(3,4-Dichlorobenzyl)-*N*-(4-methylbenzyl)piperidin-4-amine



C20 H24 Cl2 N2; Mol wt: 363.3296

ACTION – Chemokine CCR1 and/or CCR3 receptor modulator, potentially useful for the treatment of autoimmune, inflammatory, proliferative and immunologically mediated diseases. This compound was reported to antagonize the eotaxin-mediated calcium flux in human eosinophils and the MIP-1 α -mediated calcium flux in human monocytes. Other exemplified compounds from this series of substituted piperidine derivatives include the following:



Compound	R1	X	Formula
301810	4-NO2-PhCH2		C ₁₉ H ₂₁ Cl ₂ N ₃ O ₂
301811	4-quinolyl-CH2		C ₂₂ H ₂₃ Cl ₂ N ₃
301812	4,6-(Me)2-2-pyrimidinyl-SCH2CO		C ₂₀ H ₂₄ Cl ₂ N ₄ OS
301813	2-Cl-6-(cyclopropyl-NH)-4-pyrimidinyl-NHCH2CH2		C ₂₁ H ₂₇ Cl ₃ N ₆
301814	2-(4-Cl-Ph)-5-Me-4-thiazolyl-CH2CO		C ₂₄ H ₂₄ Cl ₃ N ₃ OS
301816	4-MeO-PhCH2	2HCl	C ₂₀ H ₂₄ Cl ₂ N ₂ O.2HCl

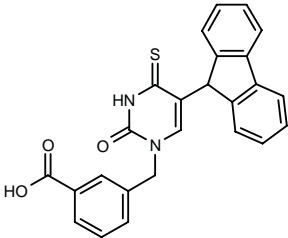
SOURCE – AstraZeneca.

REFERENCES

1. Thom, S. et al. (AstraZeneca plc) *Substd. piperidine cpds. useful as modulators of chemokine receptor activity*. WO 0114333.

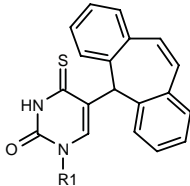
302003

3-[5-(9*H*-Fluoren-9-yl)-2-oxo-4-thioxo-1,2,3,4-tetrahydro-pyrimidin-1-ylmethyl]benzoic acid

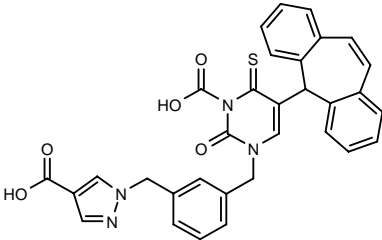


C25 H18 N2 O3 S; Mol wt: 426.4942

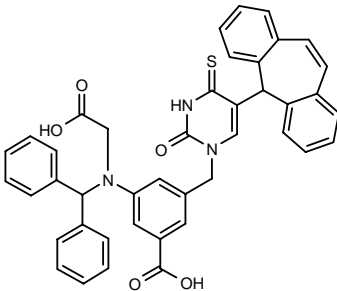
ACTION – Antiinflammatory agent, a P2-purinceptor 7-transmembrane G-protein coupled receptor, particularly P2Y₂ receptor, antagonist. Potentially useful for the treatment of a variety of conditions including asthma, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, rheumatoid arthritis, myocardial ischemia, chronic obstructive pulmonary disease, cystic fibrosis, atherosclerosis, restenosis, periodontal disease, septic shock, osteoarthritis and stroke. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	Formula
302004	3-CO2H-4-MeO-PhCH2	C ₂₈ H ₂₂ N ₂ O ₄ S
302006	3-CO2H-4-OH-PhCH2	C ₂₇ H ₂₀ N ₂ O ₄ S
302007	4-CO2H-Ph	C ₂₆ H ₁₈ N ₂ O ₃ S
302009	3-CO2H-PhCH2	C ₂₇ H ₂₀ N ₂ O ₃ S



302005: C32 H24 N4 O5 S

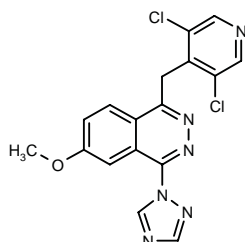


302008: C42 H33 N3 O5 S

SOURCE – AstraZeneca.

REFERENCES

1. Kindon, N. et al. (AstraZeneca plc) *Pyrimidine derivs*. US 6200981, WO 9905123.

Z-15370A***285706**1-(3,5-Dichloropyridin-4-ylmethyl)-6-methoxy-4-(1*H*-1,2,4-triazol-1-yl)phthalazine

C17 H12 Cl2 N6 O; Mol wt: 387.2288

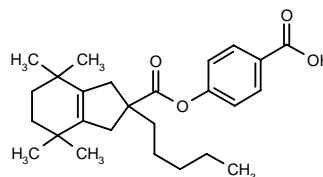
ACTION – Selective inhibitor of phosphodiesterase type 4 (PDE4; IC_{50} = 241 nM) with high selectivity versus PDE1, PDE2, PDE3 and PDE5 isozymes (IC_{50} > 1000 nM) and with lower affinity than rolapram and SB-207499 for rolapram binding sites (K_i = 383, 1.6 and 38 nM, respectively). Compound exhibited *in vitro* antiinflammatory activity, as demonstrated by inhibition of TNF- α release from human monocytes (IC_{50} = 72 nM) and ovalbumin-induced bronchoconstriction in isolated sensitized guinea pig trachea. *In vitro* in passively sensitized human airways, compound inhibited allergen-induced contractions whereas rolapram, SB-207499 and picamilast had no significant effects. *In vivo*, compound was at least equipotent to SB-207499 in inhibiting ovalbumin-induced eosinophilia in Brown-Norway rats following oral administration, but unlike the other agents, it did not induce emesis in dogs. Potentially useful for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

SOURCE – Zambon.**REFERENCES**

1. Napoletano, M. et al. (Zambon Group SpA) *Phthalazine derivs. phosphodiesterase 4 inhibitors*. EP 1097142, WO 0005218.
2. Cortijo, J. et al. *Effects of selective phosphodiesterase 4 inhibitors on allergen-induced contraction and hyperreactivity in passively sensitized human airways in vitro*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A432.
3. Ferlenga, P. et al. *Effect of Z15370A, a new PDE 4 inhibitor, on histamine and antigen induced bronchospasm in guinea pigs*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A431.
4. Morazzoni, G. et al. *Pharmacological characterization of Z15370A, a novel selective phosphodiesterase 4 inhibitor*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A431.
5. Morcillo, E.J. et al. *Effects of selective phosphodiesterase 4 inhibitors on functional response of human neutrophils and eosinophils*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A432.
6. Napoletano, M. et al. *Phthalazine PDE4 inhibitors. Part 2: The synthesis and biological evaluation of 6-methoxy-1,4-disubstituted derivatives*. Bioorg Med Chem Lett 2001, 11(1): 33.

*Identified compound **285706** (see **285699**) Drug Data Rep 2000, 022(04): 0325.

**TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY
DISEASES**

3008344-(4,4,7,7-Tetramethyl-2-pentyl-2,3,4,5,6,7-hexahydro-1*H*-inden-2-ylcarbonyloxy)benzoic acid

C26 H36 O4; Mol wt: 412.5664

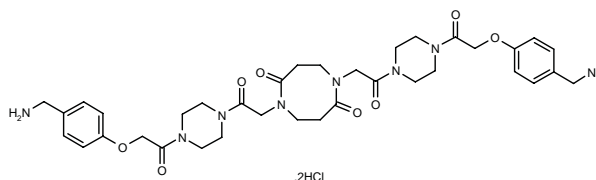
ACTION – Agent for the treatment of emphysema and related pulmonary disorders, a selective retinoic acid receptor RAR γ agonist. Compound was proven active in a rat model of elastase-induced emphysema, exhibiting 54% and 44% of alveolar repair area at 0.5 mg/kg i.p. and 1 mg/kg p.o., respectively.

SOURCE – Roche.**REFERENCES**

1. Belloni, P.N. et al. (F. Hoffmann-La Roche AG) *New selective retinoid agonists*. WO 0109076.

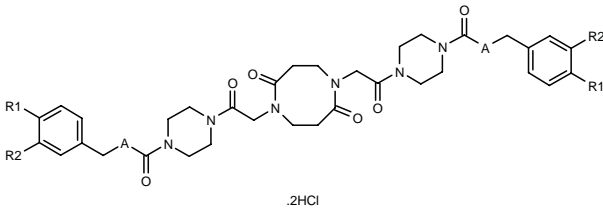
301175

1,5-Bis[2-[4-[2-[4-(aminomethyl)phenoxy]acetyl]piperazin-1-yl]-2-oxoethyl]perhydro-1,5-diazocine-2,6-dione dihydrochloride



C36 H48 N8 O8 . 2HCl; Mol wt: 793.7450

ACTION – Human tryptase inhibitor giving a K_i value of 0.0008 μ M against human lung enzyme, expected to be useful in the treatment of respiratory disorders such as bronchitis, asthma and chronic obstructive pulmonary disease (COPD). Other specifically claimed compounds from this series of perhydro-1,5-diazocine-2,6-dione derivatives are:



Compound	R1	R2	A	Formula
301179	CH2NH2	H	NH	C ₃₆ H ₅₀ N ₁₀ O ₆ .2HCl
301184	CH2NH2	H	CH2	C ₃₆ H ₅₂ N ₈ O ₆ .2HCl
301187	H	CH2NH2	CH2	C ₃₆ H ₅₂ N ₈ O ₆ .2HCl

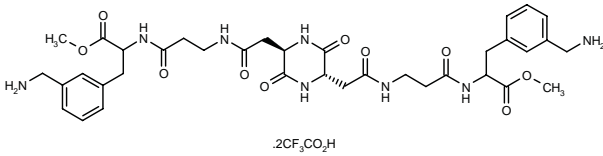
SOURCE – Byk Gulden.

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1. Baer, T. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Novel tryptase inhibitors*. WO 0110848.

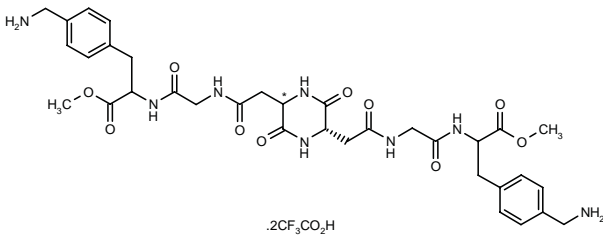
301188

N,N'-Bis[2-[*N*-[2-[3-(aminomethyl)phenyl]-1-(methoxycarbonyl)ethyl]carbamoyl]ethyl]-3,6-dioxopiperazine-2(*R*),5(*S*)-diacetamide bis(trifluoroacetate)

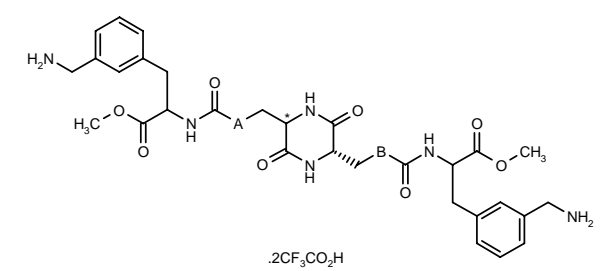


C36 H48 N8 O10 . 2 C2 H F3 O2; Mol wt: 980.8650

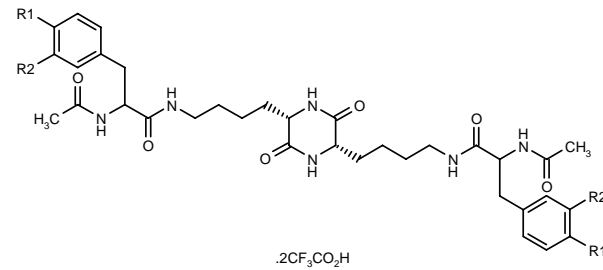
ACTION – Human tryptase inhibitor giving a *K*_i value of 0.01 μM against human lung enzyme, expected to be useful in the treatment of respiratory disorders such as bronchitis, asthma and chronic obstructive pulmonary disease (COPD). Other specifically claimed compounds from this series of diketopiperazines are:



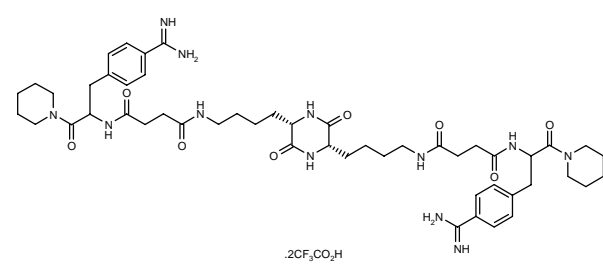
Compound	*Isomer	Formula
301192	R	C ₃₄ H ₄₄ N ₈ O ₁₀ .2C ₂ HF ₃ O ₂
301193	S	C ₃₄ H ₄₄ N ₈ O ₁₀ .2C ₂ HF ₃ O ₂



Compound	A	B	*Isomer	Formula
301194	-CH2NHCO-	-CONHCH2-	R	C ₃₄ H ₄₄ N ₈ O ₁₀ .2C ₂ HF ₃ O ₂
301195	-CH2NHCO-	-CONHCH2-	S	C ₃₄ H ₄₄ N ₈ O ₁₀ .2C ₂ HF ₃ O ₂
301196	-CH2NHCO-	-CH2-	R	C ₃₃ H ₄₃ N ₇ O ₉ .2C ₂ HF ₃ O ₂
301197	-CH2-	-CH2-	R	C ₃₂ H ₄₂ N ₆ O ₈ .2C ₂ HF ₃ O ₂
301198	-(CH2)3NHCO-	-CONH(CH2)3-	R	C ₃₈ H ₅₂ N ₈ O ₁₀ .2C ₂ HF ₃ O ₂



Compound	R1	R2	Formula
301191	CH2NH2	H	C ₃₆ H ₅₂ N ₈ O ₆ .2C ₂ HF ₃ O ₂
301199	H	CH2NH2	C ₃₆ H ₅₂ N ₈ O ₆ .2C ₂ HF ₃ O ₂



301190: C50 H72 N12 O8 . 2 C2 H F3 O2

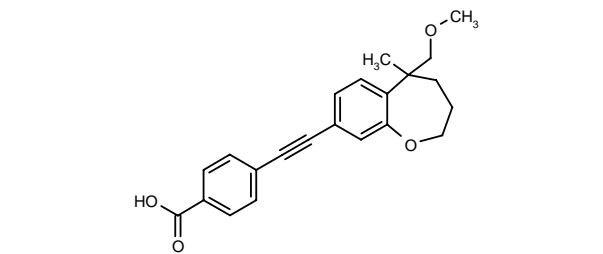
SOURCES – Byk Gulden; Max-Planck-Gesellschaft, München (DE).

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301675

4-[5-(Methoxymethyl)-5-methyl-2,3,4,5-tetrahydro-1-benzoxepin-8-yl]ethynyl]benzoic acid



C22 H22 O4; Mol wt: 350.4118

ACTION – Selective retinoic acid receptor RAR γ agonist for the treatment of emphysema and associated pulmonary disorders, proven active in a rat model of elastase-induced emphysema, where it exhibited 58% and 45.2% of alveolar repair area at 0.5 mg/kg i.p. and 0.1 mg/kg p.o., respectively.

SOURCE – Roche.

REFERENCES

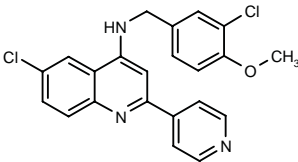
1. Belloni, P.N. and Mohr, P. (F. Hoffmann-La Roche AG) *RAR selective retinoid agonists*. WO 0114360.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

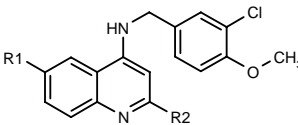
301883

6-Chloro-*N*-(3-chloro-4-methoxybenzyl)-2-(4-pyridyl)-quinolin-4-amine



C22 H17 Cl2 N3 O; Mol wt: 410.3023

ACTION – Potent and selective inhibitor of phosphodiesterase type 5 (PDE5), as demonstrated by an IC₅₀ value of 0.24 nM against PDE5 (human platelets) compared to IC₅₀ values of 10,000 nM, 1600 nM, 1500 nM and 14,000 nM, respectively, against PDE1 (canine heart), PDE2 (human platelets), PDE3 (human platelets) and PDE4 (canine kidney); IC₅₀ values of sildenafil against PDE1-5 were 2000 nM, 30,000 nM, 53,000 nM, > 1000 nM and 14 nM, respectively. In addition, it exhibited vasorelaxant effects on phenylephrine-contracted rat aortic rings (EC₅₀ = 43 nM vs. 6.1 nM for sildenafil). Potentially useful in the treatment of hypertension, heart failure, myocardial infarction, angina pectoris, arteriosclerosis, restenosis following PTCA, pulmonary hypertension, renal failure, asthma, bronchitis, dementia, glaucoma and impotence. Other exemplified compounds from this series of quinoline derivatives include the following:



Compound	R1	R2	Formula
301884	Cl	3-Pyr	C ₂₂ H ₁₇ Cl ₂ N ₃ O
301885	Cl	2-Pyr	C ₂₂ H ₁₇ Cl ₂ N ₃ O
301886	CN	4-Pyr	C ₂₃ H ₁₇ ClN ₄ O
301887	NO2	4-Pyr	C ₂₂ H ₁₇ ClN ₄ O ₃

SOURCE – Nippon Soda.

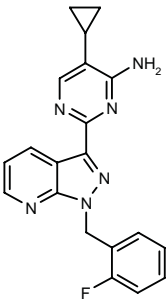
REFERENCES

1. Umeda, N. et al. (Nippon Soda Co., Ltd.) *Quinoline cpds. and process for producing the same*. WO 0112608.

BAY-41-2272*

285913

5-Cyclopropyl-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-amine



C20 H17 F N6; Mol wt: 360.3943

ACTION- Vasorelaxant agent, a guanylate cyclase stimulator proven to relax aortic rings *in vitro* (IC₅₀ = 304 nM) and to dose-dependently lower blood pressure in anesthetized rats after oral administration (0.3-3 mg/kg). Potentially useful for the treatment of cardiovascular diseases.

SOURCE – Bayer.

REFERENCES

1. Jänichen, J. et al. (Bayer AG) *Method for the production of subst. pyrimidine derivs.* DE 19942809, WO 0117998.

2. Straub, A. et al. (Bayer AG) *Subst. pyrazole derivs.* DE 19834047, EP 1102767, WO 0006568.

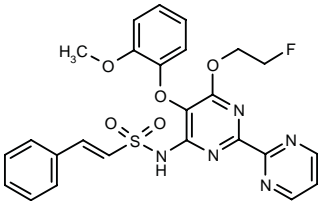
3. Starub, A. et al. *NO-independent stimulators of soluble guanylate cyclase*. Bioorg Med Chem Lett 2001, 11(6): 781.

*Identified compound **285913** Drug Data Rep 2000, 022(05): 0427.

YM-62899

303633

N-[6-(2-Fluoroethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]-2-phenylethanesulfonamide



C25 H22 F N5 O5 S; Mol wt: 523.5428

ACTION – Selective retinoic acid receptor RAR γ agonist for the treatment of emphysema and associated pulmonary disorders, proven active in a rat model of elastase-induced emphysema, where it exhibited 58% and 45.2% of alveolar repair area at 0.5 mg/kg i.p. and 0.1 mg/kg p.o., respectively.

SOURCE – Roche.

REFERENCES

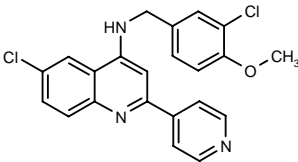
1. Belloni, P.N. and Mohr, P. (F. Hoffmann-La Roche AG) *RAR selective retinoid agonists*. WO 0114360.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

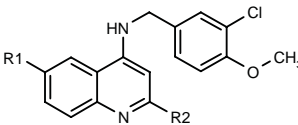
301883

6-Chloro-*N*-(3-chloro-4-methoxybenzyl)-2-(4-pyridyl)-quinolin-4-amine



C22 H17 Cl2 N3 O; Mol wt: 410.3023

ACTION – Potent and selective inhibitor of phosphodiesterase type 5 (PDE5), as demonstrated by an IC₅₀ value of 0.24 nM against PDE5 (human platelets) compared to IC₅₀ values of 10,000 nM, 1600 nM, 1500 nM and 14,000 nM, respectively, against PDE1 (canine heart), PDE2 (human platelets), PDE3 (human platelets) and PDE4 (canine kidney); IC₅₀ values of sildenafil against PDE1-5 were 2000 nM, 30,000 nM, 53,000 nM, > 1000 nM and 14 nM, respectively. In addition, it exhibited vasorelaxant effects on phenylephrine-contracted rat aortic rings (EC₅₀ = 43 nM vs. 6.1 nM for sildenafil). Potentially useful in the treatment of hypertension, heart failure, myocardial infarction, angina pectoris, arteriosclerosis, restenosis following PTCA, pulmonary hypertension, renal failure, asthma, bronchitis, dementia, glaucoma and impotence. Other exemplified compounds from this series of quinoline derivatives include the following:



Compound	R1	R2	Formula
301884	Cl	3-Pyr	C ₂₂ H ₁₇ Cl ₂ N ₃ O
301885	Cl	2-Pyr	C ₂₂ H ₁₇ Cl ₂ N ₃ O
301886	CN	4-Pyr	C ₂₃ H ₁₇ ClN ₄ O
301887	NO2	4-Pyr	C ₂₂ H ₁₇ ClN ₄ O ₃

SOURCE – Nippon Soda.

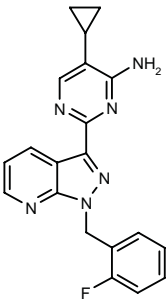
REFERENCES

1. Umeda, N. et al. (Nippon Soda Co., Ltd.) *Quinoline cpds. and process for producing the same*. WO 0112608.

BAY-41-2272*

285913

5-Cyclopropyl-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-amine



C20 H17 F N6; Mol wt: 360.3943

ACTION- Vasorelaxant agent, a guanylate cyclase stimulator proven to relax aortic rings *in vitro* (IC₅₀ = 304 nM) and to dose-dependently lower blood pressure in anesthetized rats after oral administration (0.3-3 mg/kg). Potentially useful for the treatment of cardiovascular diseases.

SOURCE – Bayer.

REFERENCES

1. Jänichen, J. et al. (Bayer AG) *Method for the production of subst. pyrimidine derivs.* DE 19942809, WO 0117998.

2. Straub, A. et al. (Bayer AG) *Subst. pyrazole derivs.* DE 19834047, EP 1102767, WO 0006568.

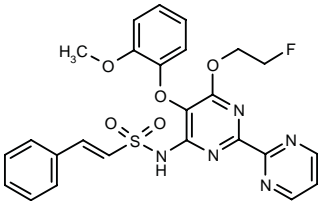
3. Starub, A. et al. *NO-independent stimulators of soluble guanylate cyclase*. Bioorg Med Chem Lett 2001, 11(6): 781.

*Identified compound **285913** Drug Data Rep 2000, 022(05): 0427.

YM-62899

303633

N-[6-(2-Fluoroethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]-2-phenylethanesulfonamide



C25 H22 F N5 O5 S; Mol wt: 523.5428

ACTION – Endothelin ET_A receptor antagonist with high selectivity for ET_A over ET_B receptors (IC₅₀ = 2.1 and 2500 nM, respectively) and *in vitro* functional antagonist activity in rat aorta ring preparations (pA₂ = 6.9). *In vivo* compound (2-3 mg/kg) showed good oral activity against the pressor response to big ET-1 in anesthetized pithed rats and in conscious normotensive rats, with a duration of activity of over 6 h in conscious animals. Potentially useful for the treatment of cardiovascular diseases such as hypertension and heart failure.

SOURCE – Yamanouchi.

REFERENCES

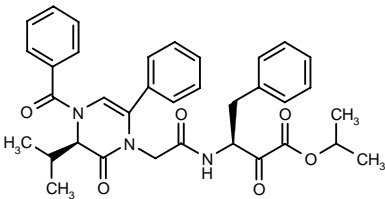
1. Harada, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Arylethanesulfonamide derivs. and drug compsn. containing the same*. EP 0882719, US 6083955, WO 9722595.

2. Harada, H. et al. *Ethenesulfonamide derivatives, a novel class of orally active endothelin-A receptor antagonists*. Chem Pharm Bull 2001, 49(5): 606.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

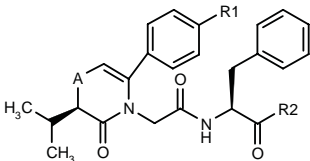
300793

3(*S*)-[2-[4-Benzoyl-3(*R*)-isopropyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrazin-1-yl]acetamido]-2-oxo-4-phenylbutyric acid isopropyl ester

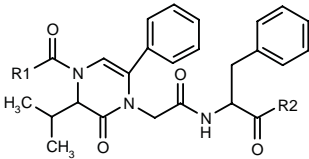


C35 H37 N3 O6; Mol wt: 595.6923

ACTION – Chymase inhibitor, as demonstrated in an *in vitro* assay using enzyme from beagle dogs (IC₅₀ = 0.20 μM), potentially useful for the treatment of myocardial infarction, cardiac hypertrophy, heart failure, arterio-sclerosis, hypertension, allergic and inflammatory diseases. Other exemplified thiazine and pyrazine derivatives include the following:



Compound	R1	R2	A	Formula
300794	H	i-PrOCO	-N(3-Pyr-CO)-	C ₃₄ H ₃₆ N ₄ O ₆
300795	H	i-PrOCO	-N(4-Pyr-CO)-	C ₃₄ H ₃₆ N ₄ O ₆
300796	H	i-PrOCO	-N(SO2Ph)-	C ₃₄ H ₃₇ N ₃ O ₇ S
300797	H	2-benzothiazolyl	-N(Ac)-	C ₃₃ H ₃₂ N ₄ O ₄ S
300809	H	4,5-dihydro-2-oxazolyl	-N(Ac)-	C ₂₉ H ₃₂ N ₄ O ₅
300811	H	4,5-dihydro-2-thiazolyl	-N(Ac)-	C ₂₉ H ₃₂ N ₄ O ₄ S
300812	H	i-PrOCO	-S-	C ₂₈ H ₃₂ N ₂ O ₅ S
300813	OMe	i-PrOCO	-S-	C ₂₉ H ₃₄ N ₂ O ₆ S



Compound	R1	R2	Formula
300814	Me	CF3	C ₂₇ H ₂₈ F ₃ N ₃ O ₄
300815	Ph	4,4-(Me)2-4,5-dihydro-2-oxazolyl	C ₃₆ H ₃₈ N ₄ O ₅

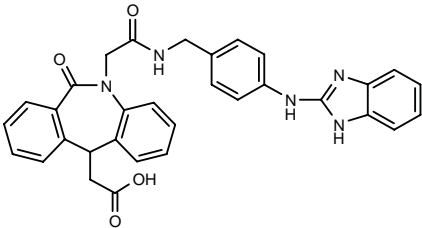
SOURCE – Santen.

REFERENCES

1. Matsumoto, E. et al. (Santen Pharmaceutical Co., Ltd.) *Novel thiazine or pyrazine derivs*. JP 2001097957, WO 0107419.

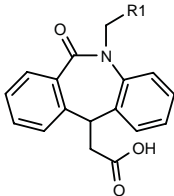
301251

2-[5-[2-[4-(1*H*-Benzimidazol-2-ylamino)benzylamino]-2-oxoethyl]-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl]acetic acid



C32 H27 N5 O4; Mol wt: 545.5963

ACTION – Integrin inhibitor with selectivity for the α_vβ₃ (vitronectin) receptor, potentially useful in the treatment of a broad range of disorders including atherosclerosis, restenosis, angioplasty, acute renal disorders, thrombosis, stroke, angiogenesis, cancer, osteoporosis, hypertension, psoriasis, viral, parasitic and bacterial infections, inflammation, hyperparathyroidism and Paget's disease. Other exemplified compounds include the following:



Compound	R1	Formula
301252	2-[NH2C(=NH)NH]-5-thiazolyl-CH2NHCO	C ₂₃ H ₂₂ N ₆ O ₄ S
301253	4-(PhCH2NHCONH)-PhCH2NHCO	C ₃₃ H ₃₀ N ₄ O ₅
301254	4-[4-(2-Pyr-NHCH2)-2-thienyl-CH2NHCO]-2-thiazolyl	C ₃₂ H ₂₇ N ₅ O ₄ S ₂

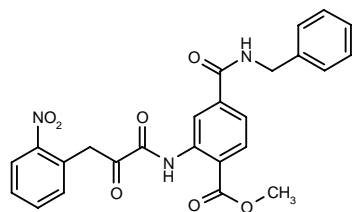
SOURCE – BASF.

REFERENCES

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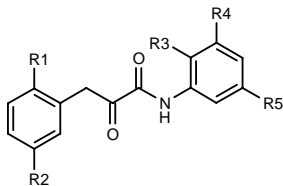
301521

4-(Benzylcarbamoyl)-2-[3-(2-nitrophenyl)-2-oxopropion-amido]benzoic acid methyl ester

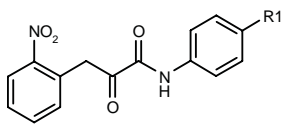


C25 H21 N3 O7; Mol wt: 475.4549

ACTION – An inhibitor of chymase that exhibited 99.0% inhibition at 0.1 mM in an *in vitro* assay using enzyme from dogs. This compound is expected to be useful for the treatment of restenosis, hypertension, arteriosclerosis, cardiac hypertrophy, heart failure and peripheral circulatory disorders, among others. Other exemplified α -ketoamide compounds are:



Compound	R1	R2	R3	R4	R5	Formula
301522	H	H	CONHCH2Ph	H	CONHCH2Ph	C ₃₁ H ₂₇ N ₃ O ₄
301525	NO2	H	CONHCH2Ph	H	CONHCH2Ph	C ₃₁ H ₂₆ N ₄ O ₆
301526	NO2	OCH2Ph	CONHCH2Ph	H	CONHCH2Ph	C ₃₈ H ₃₂ N ₄ O ₇
301529	H	H	1-(CO2Et)- -4-Pip-NHCO	H	4-morpholinyl- -CO	C ₂₉ H ₃₄ N ₄ O ₇
301531	NO2	H	H	H	H	C ₁₅ H ₁₂ N ₂ O ₄
301532	NO2	H	H	i-Pr	i-Pr	C ₂₁ H ₂₄ N ₂ O ₄
301533	NO2	H	H	H	CF3	C ₁₈ H ₁₁ F ₃ N ₂ O ₄



Compound	R1	Formula
301527	CH2CONHCH2Ph	C ₂₄ H ₂₁ N ₃ O ₅
301534	5-Me-1,3,4-thiadiazol-2-yl-NHSO2	C ₁₈ H ₁₅ N ₅ O ₆ S ₂
301535	2-thiazolyl-NHSO2	C ₁₈ H ₁₄ N ₄ O ₆ S ₂
301536	CH2CH(CO2Me)2	C ₂₁ H ₂₀ N ₂ O ₈

SOURCE – Senju.

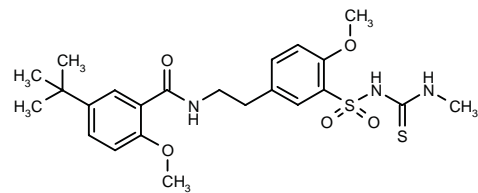
REFERENCES

1. Sai, O. et al. (Senju Pharmaceuticals Co., Ltd.) α -Ketoamide derivs. and their medicinal use. JP 2001031636.

HMR-1372

303695

5-*tert*-Butyl-2-methoxy-*N*-[2-[4-methoxy-3-(3-methylthio-ureidosulfonyl)phenyl]ethyl]benzamide



C23 H31 N3 O5 S2; Mol wt: 493.6459

ACTION – Novel cardioselective ATP-sensitive K⁺ channel blocker that has been shown to enhance cholinergic transmission in isolated tissues. In guinea pig isolated atria, compound strongly inhibited the putative parasympathetic K_{ATP} channels, while having weak inhibitory activity on the sarcolemmal K_{ATP} channels in guinea pig cardiomyocytes. In anesthetized pigs, compound at 3 mg/kg was seen to reduce ischemia-induced ventricular fibrillation and this effect was abolished by atropine but not by atenolol, indicating an involvement of the parasympathetic system in the antifibrillatory effect of compound. In another model of ischemia in rabbits subjected to 30-min occlusion followed by 3-h reperfusion, compound given i.v. as a bolus (1.4 mg/kg) 10 min prior to occlusion followed by continuous infusion at 18 μ g/kg/min reduced the ischemic heart damage, which was not modified by muscarinic blockade. Potentially useful for the treatment of acute myocardial infarction.

SOURCE – Aventis Pharma.

REFERENCES

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2. Dendorfer, A. et al. *HMR 1372, a putative inhibitor of ATP-sensitive K⁺-channels, reduces infarct size by a cholinergic mechanism*. Naunyn-Schmied Arch Pharmacol 2001, 363(4, Suppl.): Abst 283.

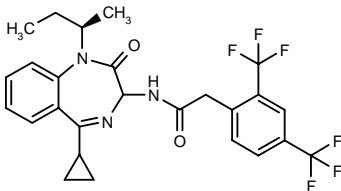
3. Kilbinger, H. et al. *Increase by the KATP channel blockers HMR 1883 and HMR 1372 of acetylcholine (ACH) release in guinea-pig isolated atria*. Naunyn-Schmied Arch Pharmacol 2001, 363(4, Suppl.): Abst 284.

4. Wirth, K.J. et al. *Atropine inhibits the antifibrillatory effect of HMR 1372, a putative blocker of cardiac vagal KATP-channels, in pigs with coronary ischemia*. Naunyn-Schmied Arch Pharmacol 2001, 363(4, Suppl.): Abst 285.

ANTIARRHYTHMIC DRUGS

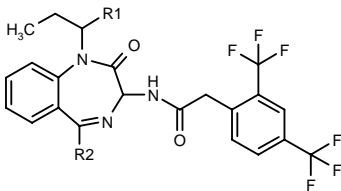
301237

(–)-2-[2,4-Bis(trifluoromethyl)phenyl]-N-[5-cyclopropyl-1-[1 (*R*)-methylpropyl]-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl]acetamide



C26 H25 F6 N3 O2; Mol wt: 525.4905

ACTION – Selective $K_{V(s)}$ channel antagonist ($IC_{50} < 100$ nM), reported to be at least 10 times more potent in the blockade of $K_{V(s)}$ than of $K_{V(r)}$ channels. Potentially useful for the treatment and prevention of cardiac arrhythmias such as atrial, supraventricular and ventricular ectopy, tachycardia, flutter or fibrillation, including atrial, supraventricular and ventricular arrhythmias resulting from myocardial ischemic injury. Other specifically claimed compounds from this series of 1*H*-1,4-benzodiazepin-2-one derivatives are:



Compound	R1	R2	Isomer	Formula
301240	(S)-Me	cyclopropyl	(+)	C ₂₆ H ₂₅ F ₆ N ₃ O ₂
301241	(S)-Me	cyclopropyl	(-)	C ₂₆ H ₂₅ F ₆ N ₃ O ₂
301242	(R)-Me	Ph	(+)	C ₂₉ H ₂₅ F ₆ N ₃ O ₂
301243	(R)-Me	Ph	(-)	C ₂₉ H ₂₅ F ₆ N ₃ O ₂
301244	(S)-Me	Ph	(+)	C ₂₉ H ₂₅ F ₆ N ₃ O ₂
301245	(S)-Me	Ph	(-)	C ₂₉ H ₂₅ F ₆ N ₃ O ₂
301246	H	Pr	(+)	C ₂₅ H ₂₅ F ₆ N ₃ O ₂
301247	H	Pr	(-)	C ₂₅ H ₂₅ F ₆ N ₃ O ₂
301248	H	Ph	(+)	C ₂₈ H ₂₃ F ₆ N ₃ O ₂
301249	H	Ph	(-)	C ₂₈ H ₂₃ F ₆ N ₃ O ₂

SOURCE – Merck & Co.

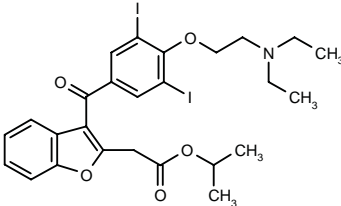
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ATI-2064¹⁻⁶

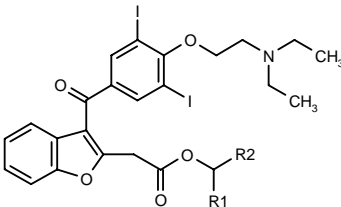
282617

2-[3-[4-[2-(Diethylamino)ethoxy]-3,5-diiodobenzoyl]-1-benzofuran-2-yl]acetic acid isopropyl ester



C26 H29 I2 N O5; Mol wt: 689.3171

ACTION – Antiarrhythmic agent, an ester homologue of amiodarone with more favorable properties in guinea pig isolated hearts, where it was more rapid and effective than the parent compound in slowing heart rate, delaying atrioventricular nodal and intraventricular conduction, and prolonging ventricular repolarization. Moreover, compound exhibited longer half-life than amiodarone in human plasma ($t_{1/2} = 30$ min). Within this series of amiodarone homologues, the following are also described:



Compound	R1	R2	Formula
ATI-2042 [282618] ¹⁻⁶	Et	Me	C ₂₇ H ₃₁ I ₂ NO ₅
ATI-2054 [282619] ¹⁻⁶	t-Bu	H	C ₂₈ H ₃₃ I ₂ NO ₅
ATI-2010 [303021] ^{1-4,6}	Me	H	C ₂₅ H ₂₇ I ₂ NO ₅

SOURCE – ARYx Therapeutics.

REFERENCES

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2. Druzgala, P. (ARYx Therapeutics, Inc.) *Cpd. for treatment of cardiac arrhythmia, synthesis, and method of use.* US 5849788.

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4. Juhasz, A. and Bodor, N. *Cardiovascular studies on different classes of soft drugs.* Pharmazie 2000, 55(3): 228.

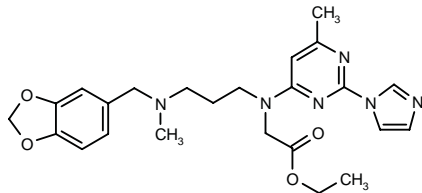
5. Juhász, A. et al. *The design, synthesis and evaluation of different soft analogs of amiodarone.* Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

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HEART FAILURE THERAPY

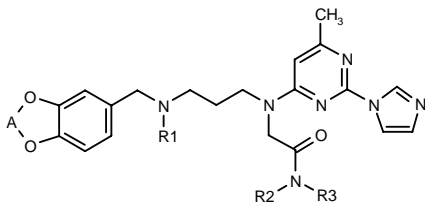
301716

2-[*N*-[3-[*N*-(1,3-Benzodioxol-5-ylmethyl)-*N*-methylamino]-propyl]-*N*-[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]-amino]acetic acid ethyl ester



C24 H30 N6 O4; Mol wt: 466.5390

ACTION – Nitric oxide synthase (NOS) inhibitor with potential for the treatment of conditions resulting from abnormal nitric oxide production, particularly multiple sclerosis, rheumatoid arthritis, dilated cardiomyopathy and congestive heart failure. Other specifically claimed compounds from this series of *N*-heterocyclic derivatives include the following:



Compound	R1	R2	R3	A	Formula
301718	Me	CH2CH2N(Me)2	H	-CH2-	C28H36N8O3
301719	H	Et	Et	-CH2-	C28H33N7O3
301720	H	Me	H	-(CH2)2-	C23H29N7O3
301721	H	H	H	-(CH2)2-	C22H27N7O3
301722	H	H	H	-CH2-	C21H25N7O3

SOURCES – Berlex; Pharmacopeia.

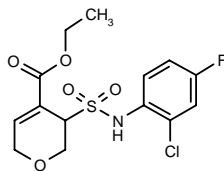
REFERENCES

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MISCELLANEOUS
CARDIOVASCULAR DRUGS

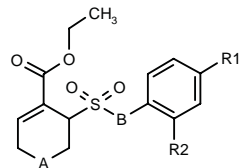
301202

3-[*N*-(2-Chloro-4-fluorophenyl)sulfamoyl]-3,6-dihydro-2*H*-pyran-4-carboxylic acid ethyl ester



C14 H15 Cl F N O5 S; Mol wt: 363.7915

ACTION – Agent for the treatment or prevention of a broad range of disorders such as cardiovascular, autoimmune, inflammatory, CNS and infectious disorders and septic shock, an inhibitor of the production of nitric oxide (NO) and cytokines. *In vitro*, compound inhibited NO production in lipopolysaccharide (LPS)- and interferon gamma-stimulated murine macrophage RAW 264.7 cells (IC₅₀ = 0.0031 μM), as well as TNF-α and IL-1β production in LPS- and interferon gamma-stimulated human monocytic P31/FUJ cells (IC₅₀ = 0.02 and 0.011 μM, respectively). *In vivo*, it gave 80% inhibition of NO production in the plasma of LPS-stimulated mice at 10 mg/kg p.o. Other exemplified compounds from this series of substituted aromatic derivatives include the following:



Compound	R1	R2	A	B	Isomer	Formula
301204	H	H	CH2	CH2		C16H20O4S
301205	OMe	H	CH2	CH2		C17H22O5S
301206	F	F	CH2	CH2		C16H18F2O4S
301208	F	Cl	CH2	CH2		C16H18ClFO4S
301209	F	Cl	CH2	CH2	(-)	C16H18ClFO4S
301210	F	Cl	CH2	CH2	(+)	C16H18ClFO4S
301212	F	F	O	NH		C14H15F2NO5S

SOURCE – Takeda.

REFERENCES

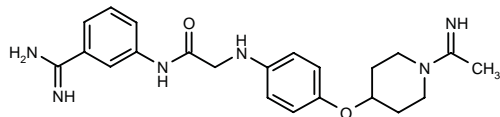
1. Tamura, N. et al. (Takeda Chemical Industries, Ltd.) *Substd. aromatic-ring cpds., process for producing the same, and use.* JP 2001114751, WO 0110826.

AGENTS AFFECTING BLOOD
COAGULATION

ANTICOAGULANTS

300962

N-(3-Amidinophenyl)-2-[4-[1-(ethanimidoyl)piperidin-4-yloxy]phenylamino]acetamide



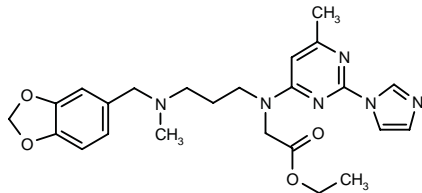
C22 H28 N6 O2; Mol wt: 408.5032

ACTION – Anticoagulant and antithrombotic agent with human factor Xa-inhibitory activity. Other specifically claimed compounds from this series of benzenamine derivatives include the following:

HEART FAILURE THERAPY

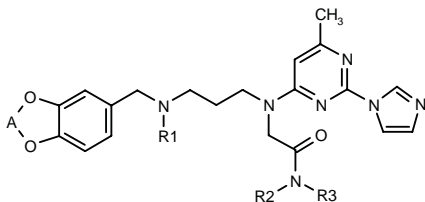
301716

2-[*N*-[3-[*N*-(1,3-Benzodioxol-5-ylmethyl)-*N*-methylamino]-propyl]-*N*-[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]-amino]acetic acid ethyl ester



C24 H30 N6 O4; Mol wt: 466.5390

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Compound	R1	R2	R3	A	Formula
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301719	H	Et	Et	-CH2-	C28H33N7O3
301720	H	Me	H	-(CH2)2-	C23H29N7O3
301721	H	H	H	-(CH2)2-	C22H27N7O3
301722	H	H	H	-CH2-	C21H25N7O3

SOURCES – Berlex; Pharmacopeia.

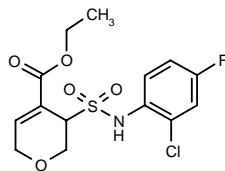
REFERENCES

1. Arnaiz, D.O. et al. (Berlex Laboratories, Inc.;Pharmacopeia, Inc.) *N-Heterocyclic derivs. as NOS inhibitors*. WO 0114371.

MISCELLANEOUS
CARDIOVASCULAR DRUGS

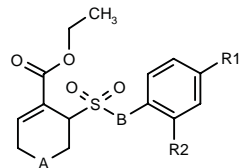
301202

3-[*N*-(2-Chloro-4-fluorophenyl)sulfamoyl]-3,6-dihydro-2*H*-pyran-4-carboxylic acid ethyl ester



C14 H15 Cl F N O5 S; Mol wt: 363.7915

ACTION – Agent for the treatment or prevention of a broad range of disorders such as cardiovascular, autoimmune, inflammatory, CNS and infectious disorders and septic shock, an inhibitor of the production of nitric oxide (NO) and cytokines. *In vitro*, compound inhibited NO production in lipopolysaccharide (LPS)- and interferon gamma-stimulated murine macrophage RAW 264.7 cells (IC₅₀ = 0.0031 μM), as well as TNF-α and IL-1β production in LPS- and interferon gamma-stimulated human monocytic P31/FUJ cells (IC₅₀ = 0.02 and 0.011 μM, respectively). *In vivo*, it gave 80% inhibition of NO production in the plasma of LPS-stimulated mice at 10 mg/kg p.o. Other exemplified compounds from this series of substituted aromatic derivatives include the following:



Compound	R1	R2	A	B	Isomer	Formula
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301205	OMe	H	CH2	CH2		C17H22O5S
301206	F	F	CH2	CH2		C16H18F2O4S
301208	F	Cl	CH2	CH2		C16H18ClFO4S
301209	F	Cl	CH2	CH2	(-)	C16H18ClFO4S
301210	F	Cl	CH2	CH2	(+)	C16H18ClFO4S
301212	F	F	O	NH		C14H15F2NO5S

SOURCE – Takeda.

REFERENCES

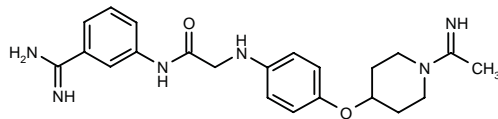
1. Tamura, N. et al. (Takeda Chemical Industries, Ltd.) *Substd. aromatic-ring cpds., process for producing the same, and use*. JP 2001114751, WO 0110826.

AGENTS AFFECTING BLOOD
COAGULATION

ANTICOAGULANTS

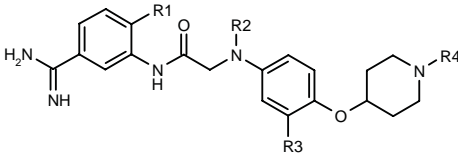
300962

N-(3-Amidinophenyl)-2-[4-[1-(ethanimidoyl)piperidin-4-yloxy]phenylamino]acetamide



C22 H28 N6 O2; Mol wt: 408.5032

ACTION – Anticoagulant and antithrombotic agent with human factor Xa-inhibitory activity. Other specifically claimed compounds from this series of benzenamine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
300963	OH	H	H	Ac	C ₂₂ H ₂₇ N ₅ O ₄
300964	H	CH ₂ CONH ₂	H	C(=NH)Me	C ₂₄ H ₃₁ N ₇ O ₃
300965	H	Me	H	C(=NH)Me	C ₂₃ H ₃₀ N ₆ O ₂
300966	OH	H	CF ₃	H	C ₂₁ H ₂₄ F ₃ N ₅ O ₃
300967	OH	H	H	Me	C ₂₁ H ₂₇ N ₅ O ₃
300968	OH	i-Pr	H	Me	C ₂₄ H ₃₃ N ₅ O ₃
300969	OH	H	CF ₃	Me	C ₂₂ H ₂₆ F ₃ N ₅ O ₃

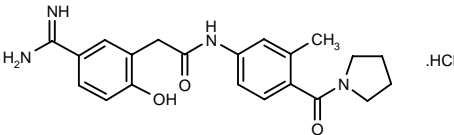
SOURCE – Berlex.

REFERENCES

1. Guilford, W.J. et al. (Berlex Laboratories, Inc.) *Benzenamine derivs. as anti-coagulants*. WO 0109093.

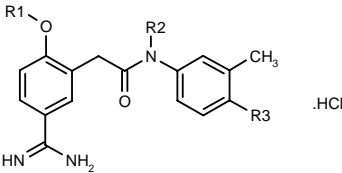
301158

2-(5-Amidino-2-hydroxyphenyl)-N-[3-methyl-4-(pyrrolidin-1-ylcarbonyl)phenyl]acetamide hydrochloride



C₂₁ H₂₄ N₄ O₃ . HCl; Mol wt: 416.9065

ACTION – Antithrombotic agent, a factor Xa inhibitor (IC₅₀ = 0.030 μM for inhibition of human factor Xa). No toxic side effects were observed at therapeutic doses. Other specifically claimed carboxamides are:



Compound	R1	R2	R3	Formula
301161	CH ₂ Ph	CH ₂ CH ₂ CO ₂ Et	1-pyrrolidinyl-CO	C ₃₃ H ₃₈ N ₄ O ₅ .HCl
301163	H	CH ₂ CH ₂ CO ₂ Et	1-pyrrolidinyl-CO	C ₂₆ H ₃₂ N ₄ O ₅ .HCl
301164	H	CH ₂ CH ₂ CO ₂ H	1-pyrrolidinyl-CO	C ₂₄ H ₂₈ N ₄ O ₅ .HCl
301165	H	H	1-Pip-CO	C ₂₂ H ₂₆ N ₄ O ₃ .HCl
301167	H	H	2-(NH ₂ SO ₂)-Ph	C ₂₂ H ₂₂ N ₄ O ₄ S.HCl

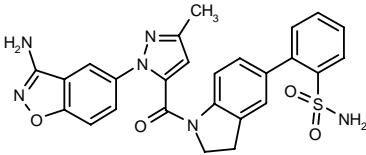
SOURCE – Boehringer Ingelheim.

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1. Ries, U. et al. (Boehringer Ingelheim Pharma KG) *Carboxylic acid amides, their production and their use as drugs*. DE 19937494, WO 0110823.

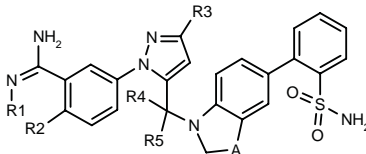
301417

2-[1-[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-methyl-1H-pyrazol-5-ylcarbonyl]-2,3-dihydro-1H-indol-5-yl]benzene-sulfonamide

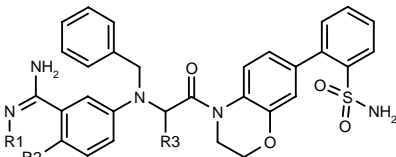


C₂₆ H₂₂ N₆ O₄ S; Mol wt: 514.5638

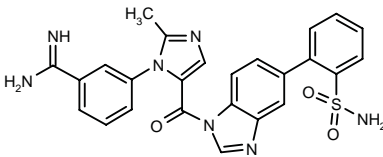
ACTION – Potent and selective factor Xa inhibitor that is reported to show selectivity for factor Xa versus other proteases involved in the coagulation and fibrinolytic cascades and is thus useful for the treatment of coagulation disorders. Other specifically claimed compounds are:



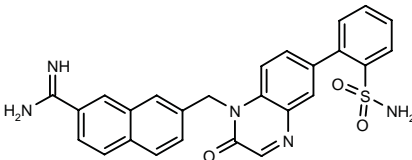
Compound	R1	R2	R3	R4	R5	A	Formula
301418	-O-	Me	-O-			-(CH ₂) ₂ -	C ₂₇ H ₂₄ N ₆ O ₄ S
301420	-O-	Me	-O-			-CH ₂ N(CO ₂ Me)-	C ₂₈ H ₂₆ N ₇ O ₆ S
301428	H	H	CF ₃	H	H	CH ₂	C ₂₆ H ₂₃ F ₃ N ₆ O ₂ S



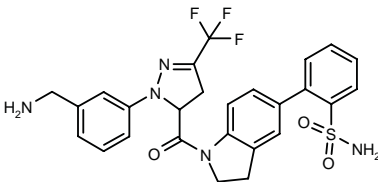
Compound	R1	R2	R3	Formula
301424	H	H	Ph	C ₃₆ H ₃₃ N ₅ O ₄ S
301426		-NH-	cyclohexyl-CH ₂	C ₃₇ H ₄₀ N ₆ O ₄ S



301422: C₂₅ H₂₁ N₇ O₃ S



301427: C₂₆ H₂₁ N₅ O₃ S



301429: C₂₆ H₂₄ F₃ N₅ O₃ S

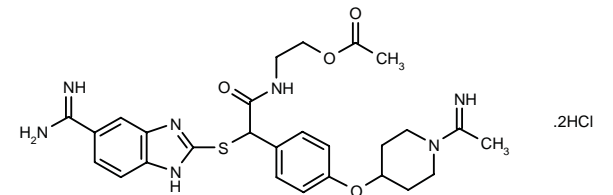
SOURCE – COR Therapeutics.

REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Inhibitors of factor Xa*. WO 0112600.

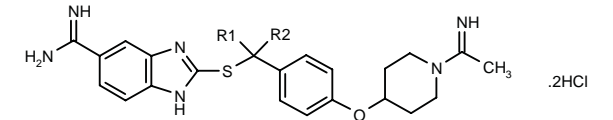
301511

Acetic acid 2-[2-(5-amidino-1*H*-benzimidazol-2-ylsulfan-yl)-2-[4-[1-(1-iminoethyl)piperidin-4-yloxy]phenyl]-acetamido]ethyl ester dihydrochloride



C27 H33 N7 O4 S . 2HCl; Mol wt: 624.5905

ACTION – Antithrombotic agent that selectively inhibits factor Xa with 12, 77 and > 95% inhibition at 0.01, 0.1 and 1 μM, respectively, versus < 10% inhibition of thrombin at 0.1 mM. Other exemplified aromatic amidine compounds are:



Compound	R1	R2	Formula
301513	H	H	C ₂₂ H ₂₆ N ₆ O ₅ .2HCl
301514	CH ₂ OAc	H	C ₂₈ H ₃₀ N ₆ O ₃ S.2HCl
301515	CH(Me)OAc	H	C ₂₈ H ₃₂ N ₆ O ₃ S.2HCl
301516	CH ₂ OAc	Et	C ₂₇ H ₃₄ N ₆ O ₃ S.2HCl
301517	-(CH ₂) ₃ CH(OAc)-		C ₂₈ H ₃₄ N ₆ O ₃ S.2HCl

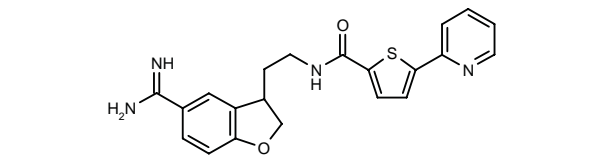
SOURCE – Toa Eiyo.

REFERENCES

1. Sato, H. et al. (Toa Eiyo Ltd.) *Novel aromatic amidine derivs. and their salts*. JP 2001019678.

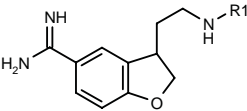
301841

N-[2-(5-Amidino-2,3-dihydro-1-benzofuran-3-yl)ethyl]-5-(2-pyridyl)thiophene-2-carboxamide



C21 H20 N4 O2 S; Mol wt: 392.4810

ACTION – Anticoagulant, a factor Xa inhibitor. Other specifically claimed compounds from this series of substituted (aminoiminomethyl or aminomethyl) dihydro-benzofurans and benzopyrans include the following:



Compound	R1	Formula
301844	4-[NH ₂ CH ₂ C(Me) ₂]-PhCO	C ₂₂ H ₂₈ N ₄ O ₂
301846	COC(Ph) ₂ Me	C ₂₆ H ₂₇ N ₃ O ₂
301847	4-CN-PhOC(Me) ₂ CO	C ₂₂ H ₂₄ N ₄ O ₃
301848	4-oxo-4,5,6,7-tetrahydro-3-benzofuryl-CO	C ₂₀ H ₂₁ N ₃ O ₄
301849	4-Cl-1,3-(Me) ₂ -1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-5-yl-CO	C ₂₀ H ₂₁ ClN ₆ O ₂
301850	5-Me-2-indolyl-CO	C ₂₁ H ₂₂ N ₄ O ₂
301851	4-[3-(NH ₂ CH ₂)-Ph]-PhCO	C ₂₅ H ₂₆ N ₄ O ₂
301853	7-Cl-2,1,3-benzoxadiazol-5-yl-SO ₂	C ₁₇ H ₁₆ ClN ₅ O ₄ S

SOURCE – Aventis Pharma.

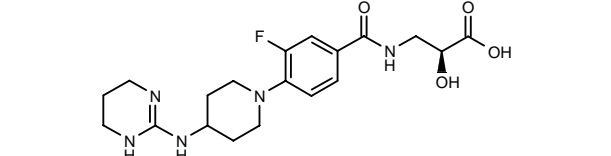
REFERENCES

1. Burns, C.J. et al. (Aventis Pharmaceuticals, Inc.) *Subst. (aminoiminomethyl or aminomethyl) dihydrobenzofurans and benzopyrans*. WO 0114358.

ANTIPLATELET THERAPY

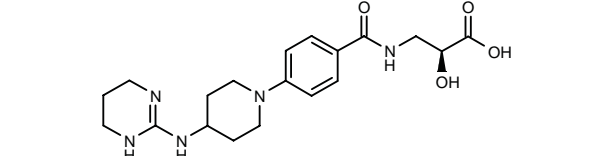
301255

3-[3-Fluoro-4-[4-(1,4,5,6-tetrahydropyrimidin-2-ylamino)-piperidin-1-yl]benzamido]-2(*S*)-hydroxypropionic acid



C19 H26 F N5 O4; Mol wt: 407.4434

ACTION – Potent dual integrin α_vβ₃ and fibrinogen gpIIb/IIIa receptor antagonist (IC₅₀ = 2.8 and 12 nM, respectively), also reported to inhibit human platelet aggregation. Potentially useful for the treatment of cardiovascular and cerebrovascular disorders, thrombo-embolic disorders, neovascularization-related disorders, cancer, immune diseases and bone disorders. Another compound from this series of ω-amino-α-hydroxycarboxylic acid derivatives is:



301257: C19 H27 N5 O4

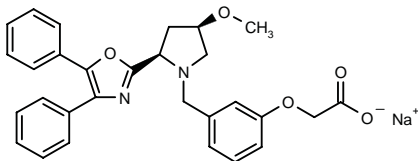
SOURCE – Meiji Seika.

REFERENCES

1. Ajito, K. et al. (Meiji Seika Kaisha, Ltd.) *ω-Amino-α-hydroxycarboxylic acid derivs. having integrin α_vβ₃ antagonism*. WO 0110844.

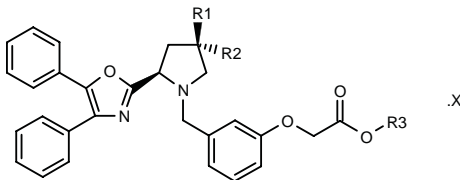
302010

2-[3-[2(*R*)-(4,5-Diphenyloxazol-2-yl)-4(*R*)-methoxy-pyrrolidin-1-ylmethyl]phenoxy]acetic acid sodium salt



C29 H27 N2 Na O5; Mol wt: 506.5313

ACTION – Prostaglandin I₂ (PGI₂) agonist with potential for the treatment or prevention of arterial obstruction, restenosis or ischemic complications after coronary angioplasty, arteriosclerosis, cerebrovascular disease, ischemic heart disease, dermatosis and hepatic insufficiency. *In vitro*, compound inhibited ADP-induced aggregation of human platelet-rich plasma (PRP) with an IC₅₀ value < 0.1 μM. Other specifically claimed compounds from this series of 4,5-diaryloxazole derivatives are:



Compound	R1	R2	R3	X	Formula
302011	H	OMe	Na		C ₂₉ H ₂₇ N ₂ NaO ₅
302012	OH	H	Et		C ₃₀ H ₃₀ N ₂ O ₅
302013	H	OH	Et		C ₃₀ H ₃₀ N ₂ O ₅
302014	OMe	H	Et		C ₃₁ H ₃₂ N ₂ O ₅
302015	H	OMe	Et		C ₃₁ H ₃₂ N ₂ O ₅
302016	OH	H	Na		C ₂₈ H ₂₅ N ₂ NaO ₅
302017	-O-		Na		C ₂₈ H ₂₃ N ₂ NaO ₅
302018	H	OH	Na		C ₂₈ H ₂₅ N ₂ NaO ₅
302019	-O-		Et		C ₃₀ H ₂₈ N ₂ O ₅
302020	H	OMe	H		C ₂₉ H ₂₈ N ₂ O ₅
302021	H	OMe	H	L-tartrate	C ₂₉ H ₂₈ N ₂ O ₅ ·C ₄ H ₆ O ₆

SOURCE – Fujisawa.

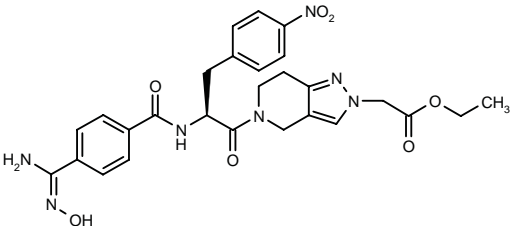
REFERENCES

1. Hattori, K. and Tanaka, A. (Fujisawa Pharmaceutical Co., Ltd.) 4,5-Diaryloxazole cpds. with prostaglandin I₂ (PGI₂) agonistic activity. WO 0116132.

UR-3216¹⁻⁹

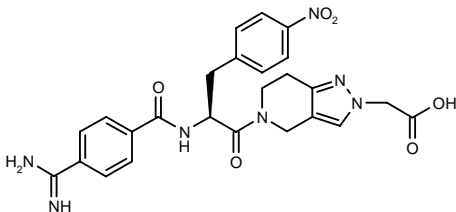
276198

2-[5-[*N*-[4-(Hydroxyamidino)benzoyl]-4-nitro-L-phenyl-alanyl]-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*c*]pyridin-2-yl]acetic acid ethyl ester



C27 H29 N7 O7; Mol wt: 563.5681

ACTION – Antiplatelet agent, a double prodrug of the active platelet gpIIb/IIIa receptor antagonist **UR-2922**, which showed high binding affinity for both resting and activated human platelets (K_i < 1 nM), high selectivity relative to the α_vβ₃ receptor and a dissociation rate from resting platelets of 95 min The active compound also strongly inhibited the aggregation of human platelets induced by a variety of agonists including ADP, collagen, U-46619, thrombin or thrombin receptor-activating peptide (IC₅₀ = 24-31 nM). *In vivo*, the prodrug showed high and long-lasting (> 20 h) oral antiplatelet efficacy, inhibiting on platelet aggregation at doses of 0.03-0.3 mg/kg in dogs and monkeys, without excessive bleeding or thrombocytopenia. In a guinea pig model of photochemically induced carotid artery thrombosis, the active compound UR-2922 given i.v. significantly increased the time to occlusion at doses of 10 μg/kg or more. The prodrug exhibited a superior oral antiplatelet profile compared to other antiplatelet drugs such as xemilofiban, orbofiban and sibrifiban. The prodrug showed a good pharmacokinetic profile, with oral bioavailability of 69% in dogs, and rapid conversion to the active compound UR-2922 was seen after both oral and i.v. administration of the prodrug. Potentially useful for the treatment of cardiovascular diseases.



UR-2922 [276199]:^{1,3-5,7-9} C25 H25 N7 O6

SOURCE – Ube.

REFERENCES

1. Kuroki, Y. et al. (Ube Industries, Ltd.) *N*-Acylamino acid amide cpds. and intermediates for preparation thereof. EP 1020467, US 6265418, WO 9906402.

2. Aga, Y. et al. A novel oral GPIIb/IIIa antagonist, UR-3216. (2). *In vivo* efficacy and prolongation of bleeding. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-283.

3. Baba, K. et al. A novel GPIIb/IIIa antagonist, UR-3216. (1). *Studies of the active form, UR-2922*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-284.

4. Baba, K. et al. *In vitro* and *in vivo* pharmacology of UR-3216, a novel GPIIb/IIIa antagonist. Thromb Haemost 1999, (Suppl.): Abst 2117.

5. Baba, K. et al. *UR-3216: A manageable oral GPIIb/IIIa antagonist*. Cardiovasc Drug Rev 2001, 19(1): 25.

6. Cox, D. et al. *UR-3216: An oral GPIIb/IIIa antagonist with abciximab-like properties*. Thromb Haemost 2001, (Suppl.): Abst P1633.

7. Nakanishi, T. et al. *A novel, oral GPIIb/IIIa antagonist, UR-3216. (3) Pharmacokinetics: Bioavailability and food-effect*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-287.

8. Noriko, T. et al. *Specific inhibiting characteristics of orally available anti-GP IIb/IIIa agent UR-3216 on shear-induced von Willebrand factor-mediated platelet ctivation and thrombus formation*. Cardiovasc Drugs Ther 2001, 15(Suppl. 1): Abst P046.

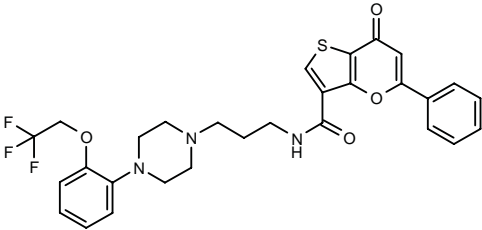
9. Ueno, H. et al. *UR-3216, a novel GPIIb/IIIa antagonist*. Thromb Haemost 1999, (Suppl.): Abst 2116.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

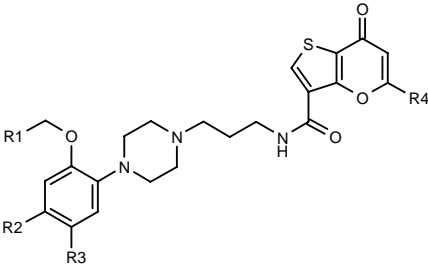
300943

7-Oxo-5-phenyl-*N*-[3-[4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl]propyl]-7*H*-thieno[3,2-*b*]pyran-3-carboxamide



C29 H28 F3 N3 O4 S; Mol wt: 571.6172

ACTION – Potent and selective α_1 -adrenoceptor antagonist devoid of hypotensive activity, with potential for the treatment of obstructive syndromes of the lower urinary tract including benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS) and neurogenic lower urinary tract dysfunction (NLUTD), as well as for lowering intraocular pressure and for the treatment of cardiac arrhythmia and erectile and sexual dysfunction. *In vitro*, compound gave K_i values of 0.045, 4.34, 1.01 and 7.59 nM, respectively, for cloned human α_{1A} , α_{1B} , α_{1D} and 5-HT $_{1A}$ receptors; K_i values for prazosin in this assay were 0.61, 0.42, 0.23 and > 10,000 nM, respectively. In addition, it was shown to antagonize noradrenaline-induced contractions of rabbit aorta rings pretreated with chloroethylclonidine with a pK_b value of 9.12, being more potent than prazosin (pK_b = 8.11). Uroselectivity was demonstrated *in vivo* in dogs by an ID_{50} value of 2.7 μ g/kg i.v. for inhibition of noradrenaline-induced urethral contractions, compared to an ED_{25} value of > 1000 μ g/kg i.v. for lowering blood pressure. In this model, prazosin exhibited an ID_{50} value of 3.6 μ g/kg i.v. and an ED_{25} value of 6.6 μ g/kg i.v. Other specifically claimed compounds from this series of thieno-pyranecarboxamide derivatives are:



Compound	R1	R2	R3	R4	Formula
300944	H	H	Cl	Ph	C ₂₈ H ₂₈ ClN ₃ O ₄ S
300945	H	H	H	Ph	C ₂₈ H ₂₉ N ₃ O ₄ S
300946	H	H	H	cyclohexyl	C ₂₈ H ₃₅ N ₃ O ₄ S
300947	H	H	H	CF ₃	C ₂₃ H ₂₄ F ₃ N ₃ O ₄ S
300948	H	H	OCH ₂ CF ₃	Ph	C ₃₀ H ₃₀ F ₃ N ₃ O ₅ S
300949	CF ₃	F	H	Ph	C ₂₉ H ₂₇ F ₄ N ₃ O ₄ S

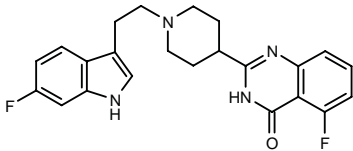
SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Thienopyranecarboxamide derivs*. WO 0109140.

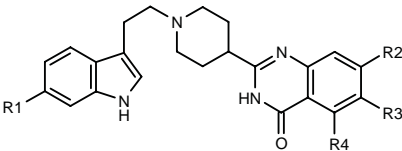
301169

5-Fluoro-2-[1-[2-(6-fluoro-1*H*-indol-3-yl)ethyl]piperidin-4-yl]quinazolin-4(3*H*)-one



C23 H22 F2 N4 O; Mol wt: 408.4498

ACTION – Agent for the treatment of urinary tract disorders such as benign prostatic hypertrophy (BPH), as well as for the treatment of pain, a selective α_{1A} - and α_{1B} -adrenoceptor antagonist, as demonstrated in binding assays by pK_i values of 9.36, 8.87 and 7.65, respectively, for α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors transfected in CHO-K1 cells. Other specifically claimed compounds from this series of quinazolinone and azaquinazolinone derivatives are:



Compound	R1	R2	R3	R4	Formula
301170	H	H	H	H	C ₂₃ H ₂₄ N ₄ O
301171	H	H	Cl	H	C ₂₃ H ₂₃ ClN ₄ O
301173	H	Cl	H	H	C ₂₃ H ₂₃ ClN ₄ O
301174	H	F	H	H	C ₂₃ H ₂₃ FN ₄ O
301176	H	F	F	H	C ₂₃ H ₂₂ F ₂ N ₄ O
301177	F	H	H	H	C ₂₃ H ₂₃ FN ₄ O
301178	F	H	H	Cl	C ₂₃ H ₂₂ ClFN ₄ O
301180	F	H	Cl	H	C ₂₃ H ₂₂ ClFN ₄ O

5. Baba, K. et al. *UR-3216: A manageable oral GPIIb/IIIa antagonist*. Cardiovasc Drug Rev 2001, 19(1): 25.

6. Cox, D. et al. *UR-3216: An oral GPIIb/IIIa antagonist with abciximab-like properties*. Thromb Haemost 2001, (Suppl.): Abst P1633.

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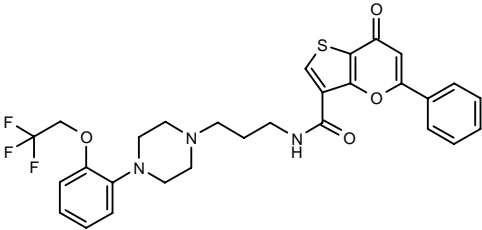
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RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

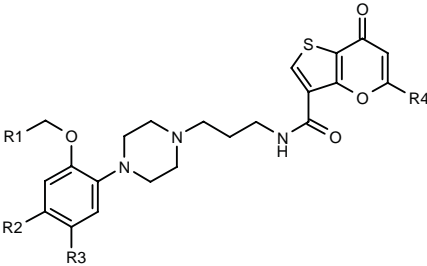
300943

7-Oxo-5-phenyl-*N*-[3-[4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl]propyl]-7*H*-thieno[3,2-*b*]pyran-3-carboxamide



C29 H28 F3 N3 O4 S; Mol wt: 571.6172

ACTION – Potent and selective α_1 -adrenoceptor antagonist devoid of hypotensive activity, with potential for the treatment of obstructive syndromes of the lower urinary tract including benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS) and neurogenic lower urinary tract dysfunction (NLUTD), as well as for lowering intraocular pressure and for the treatment of cardiac arrhythmia and erectile and sexual dysfunction. *In vitro*, compound gave K_i values of 0.045, 4.34, 1.01 and 7.59 nM, respectively, for cloned human α_{1A} , α_{1B} , α_{1D} and 5-HT $_{1A}$ receptors; K_i values for prazosin in this assay were 0.61, 0.42, 0.23 and > 10,000 nM, respectively. In addition, it was shown to antagonize noradrenaline-induced contractions of rabbit aorta rings pretreated with chloroethylclonidine with a pK_b value of 9.12, being more potent than prazosin (pK_b = 8.11). Uroselectivity was demonstrated *in vivo* in dogs by an ID_{50} value of 2.7 μ g/kg i.v. for inhibition of noradrenaline-induced urethral contractions, compared to an ED_{25} value of > 1000 μ g/kg i.v. for lowering blood pressure. In this model, prazosin exhibited an ID_{50} value of 3.6 μ g/kg i.v. and an ED_{25} value of 6.6 μ g/kg i.v. Other specifically claimed compounds from this series of thieno-pyranecarboxamide derivatives are:



Compound	R1	R2	R3	R4	Formula
300944	H	H	Cl	Ph	C ₂₈ H ₂₈ ClN ₃ O ₄ S
300945	H	H	H	Ph	C ₂₈ H ₂₉ N ₃ O ₄ S
300946	H	H	H	cyclohexyl	C ₂₈ H ₃₅ N ₃ O ₄ S
300947	H	H	H	CF ₃	C ₂₃ H ₂₄ F ₃ N ₃ O ₄ S
300948	H	H	OCH ₂ CF ₃	Ph	C ₃₀ H ₃₀ F ₃ N ₃ O ₅ S
300949	CF ₃	F	H	Ph	C ₂₉ H ₂₇ F ₄ N ₃ O ₄ S

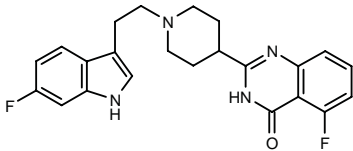
SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Thienopyranecarboxamide derivs*. WO 0109140.

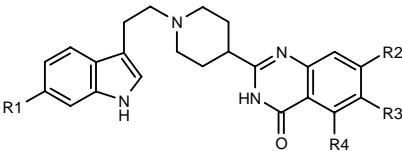
301169

5-Fluoro-2-[1-[2-(6-fluoro-1*H*-indol-3-yl)ethyl]piperidin-4-yl]quinazolin-4(3*H*)-one



C23 H22 F2 N4 O; Mol wt: 408.4498

ACTION – Agent for the treatment of urinary tract disorders such as benign prostatic hypertrophy (BPH), as well as for the treatment of pain, a selective α_{1A} - and α_{1B} -adrenoceptor antagonist, as demonstrated in binding assays by pK_i values of 9.36, 8.87 and 7.65, respectively, for α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors transfected in CHO-K1 cells. Other specifically claimed compounds from this series of quinazolinone and azaquinazolinone derivatives are:



Compound	R1	R2	R3	R4	Formula
301170	H	H	H	H	C ₂₃ H ₂₄ N ₄ O
301171	H	H	Cl	H	C ₂₃ H ₂₃ ClN ₄ O
301173	H	Cl	H	H	C ₂₃ H ₂₃ ClN ₄ O
301174	H	F	H	H	C ₂₃ H ₂₃ FN ₄ O
301176	H	F	F	H	C ₂₃ H ₂₂ F ₂ N ₄ O
301177	F	H	H	H	C ₂₃ H ₂₃ FN ₄ O
301178	F	H	H	Cl	C ₂₃ H ₂₂ ClFN ₄ O
301180	F	H	Cl	H	C ₂₃ H ₂₂ ClFN ₄ O

Compound	R1	R2	R3	R4	Formula
301181	F	Cl	H	H	C ₂₃ H ₂₂ ClFN ₄ O
301182	F	H	F	H	C ₂₃ H ₂₂ F ₂ N ₄ O
301183	F	F	H	H	C ₂₃ H ₂₂ F ₂ N ₄ O
301185	F	F	F	H	C ₂₃ H ₂₁ F ₃ N ₄ O
301186	F	OMe	OMe	H	C ₂₅ H ₂₇ FN ₄ O ₃

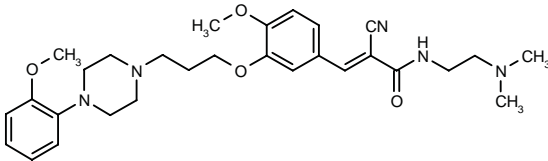
SOURCE – Roche.

REFERENCES

1. Clark, R.D. and O'Yang, C. (F. Hoffmann-La Roche AG) *Quinazolinone and azaquinazolinone derivs.* US 6258819, WO 0110860.

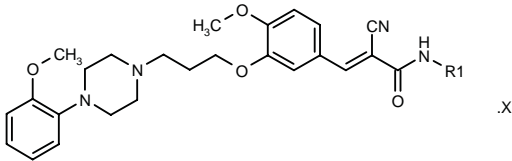
301946

2-Cyano-*N*-[2-(dimethylamino)ethyl]-3-[4-methoxy-3-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy]phenyl]-2(*E*)-propenamide

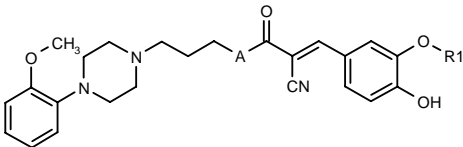


C29 H39 N5 O4; Mol wt: 521.6581

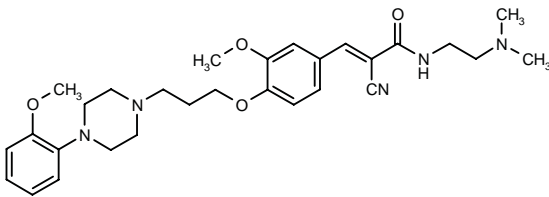
ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH), an α_1 -adrenoceptor antagonist, as demonstrated in a binding assay by 100% inhibition of [³H]-prazosin binding in rat brain membranes at 100 nM. In addition, compound was shown to produce 100% inhibition of the proliferation of murine fibroblast NIH 3T3 cells at 100 μ M. Within this series of cinnamic acid nitriles, the following compounds are also included:



Compound	R1	X	Formula
301947	H	HCl	C ₂₅ H ₃₀ N ₄ O ₄ ·HCl
301949	CH ₂ CONH ₂		C ₂₇ H ₃₃ N ₅ O ₅
301950	4-morpholinyl-CH ₂ CH ₂	2HCl	C ₃₁ H ₄₁ N ₆ O ₅ ·2HCl



Compound	R1	A	Formula
301952	H	O	C ₂₄ H ₂₇ N ₃ O ₅
301953	Me	NH	C ₂₅ H ₃₀ N ₄ O ₄



301948: C29 H39 N5 O4

SOURCE – Schwabe.

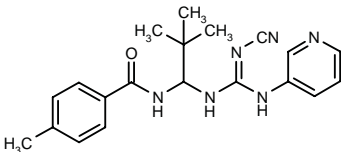
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TREATMENT OF URINARY INCONTINENCE

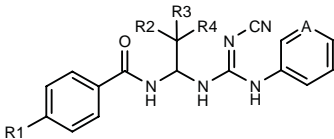
301105

N-[1-[2-Cyano-3-(3-pyridyl)guanidino]-2,2-dimethylprop-yl]-4-methylbenzamide



C20 H24 N6 O; Mol wt: 364.4506

ACTION – Potassium channel opener that showed 88% maximal steady-state membrane hyperpolarization relative to the reference compound P1075 (assigned 100%) and an EC₅₀ of 0.57 nM in guinea pig urinary bladder cells. The compound was also active in reducing stimulated contractions *in vitro* using isolated pig bladder strips and *in vivo* in a rat isovolumetric contraction model, in which a dose required to reduce the area under the curve by 30% relative to control of 0.28 mg/kg i.v. was determined. This compound is useful for the treatment of bladder overactivity, benign prostatic hyperplasia, dysmenorrhea, premature labor, urinary incontinence, male and female sexual dysfunction, as well as asthma, epilepsy, Raynaud's syndrome, intermittent claudication, migraine, pain, etc. Other exemplified compounds include the following:



Compound	R1	R2=R3=R4	Formula
301106	Me	Cl	C ₁₈ H ₁₆ Cl ₃ N ₅ O
301107	Cl	Me	C ₁₉ H ₂₁ ClN ₆ O

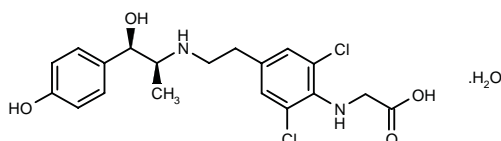
SOURCE – Abbott.

REFERENCES

1. Altenbach, R.J. et al. (Abbott Laboratories Inc.) *Potassium channel openers*. WO 0109096.

302704

2-[2,6-Dichloro-4-[2-[2(*R*)-hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methylethylamino]ethyl]phenylamino]acetic acid hydrate



C19 H22 Cl2 N2 O4 . H2O; Mol wt: 431.3136

ACTION – Potent and selective β_3 -adrenoceptor agonist with excellent selectivity over β_1 and β_2 subtypes. Compound produced potent β_3 -adrenoceptor-mediated relaxation of ferret detrusor ($EC_{50} = 14$ nM), and it significantly reduced urinary bladder pressure in anesthetized male rats ($ED_{50} = 48$ μ g/kg). Compound had no effect on heart rate or blood pressure. Potentially useful for the treatment of urinary incontinence.

SOURCE – Kissei.

REFERENCES

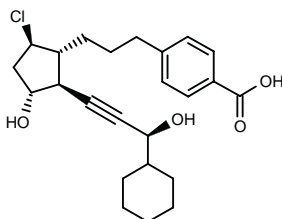
1. Tamai, T. et al. (Kissei Pharmaceutical Co., Ltd.) *Phenylaminoalkylcarboxylic acid derivs. and medicinal compns. containing the same*. EP 1043308, WO 9931045.

2. Tanaka, N. et al. *Discovery of novel N-phenylglycine derivatives as potent and selective β_3 -adrenoceptor agonists for the treatment of frequent urination and urinary incontinence*. J Med Chem 2001, 44(9): 1436.

TREATMENT OF RENAL DISEASES

301879

9 β -Chloro-15-cyclohexyl-9-deoxy-2,3,4,16,17,18,19,20-octanor-13,14-didehydro-1,5-inter-*p*-phenyleneprostaglandin F_{1 β}



C24 H31 Cl O4; Mol wt: 418.9579

ACTION – A representative compound from a series of prostaglandin derivatives with prostaglandin D₂ (PGD₂)-like agonist activity, proven to increase cAMP production *in vitro* in bovine fetal trachea-derived cells. Potentially useful in the treatment of nephropathies, as well as cardiovascular disorders such as ischemic cardiopathy, hypertension and heart failure.

SOURCE – Taisho.

REFERENCES

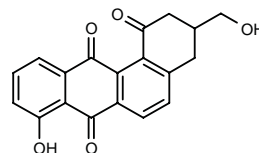
1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin derivs*. WO 0112596.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

301486

8-Hydroxy-3-(hydroxymethyl)-1,2,3,4,7,12-hexahydro-benzo[*a*]anthracene-1,7,12-trione



C19 H14 O5; Mol wt: 322.3146

ACTION – Antiulcer agent isolated from *Streptomyces* sp. Q57219 (FERM P-17283) that acts by virtue of its selective antibacterial activity against *Helicobacter pylori* (MIC = 0.2 μ g/ml); MICs against other bacteria including aerobic and anaerobic microorganisms such as *Staphylococcus aureus* FDA209P, *Escherichia coli* strains and *Pseudomonas aeruginosa* NCTC10490 are > 12.5 μ g/ml.

SOURCE – Yamanouchi.

REFERENCES

1. Taniguchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Benzo[*a*]anthracene-1,7,12-trione derivs*. JP 2001019656.

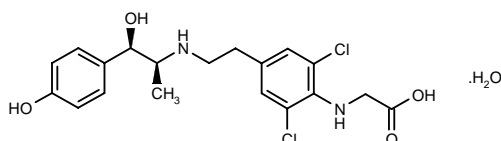
SOURCE – Abbott.

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302704

2-[2,6-Dichloro-4-[2-[2(*R*)-hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methylethylamino]ethyl]phenylamino]acetic acid hydrate



C19 H22 Cl2 N2 O4 . H2O; Mol wt: 431.3136

ACTION – Potent and selective β_3 -adrenoceptor agonist with excellent selectivity over β_1 and β_2 subtypes. Compound produced potent β_3 -adrenoceptor-mediated relaxation of ferret detrusor ($EC_{50} = 14$ nM), and it significantly reduced urinary bladder pressure in anesthetized male rats ($ED_{50} = 48$ μ g/kg). Compound had no effect on heart rate or blood pressure. Potentially useful for the treatment of urinary incontinence.

SOURCE – Kissei.

REFERENCES

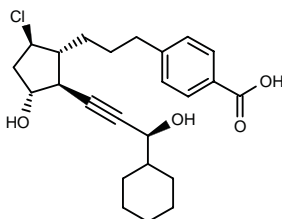
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TREATMENT OF RENAL DISEASES

301879

9 β -Chloro-15-cyclohexyl-9-deoxy-2,3,4,16,17,18,19,20-octanor-13,14-didehydro-1,5-inter-*p*-phenyleneprostaglandin F_{1 β}



C24 H31 Cl O4; Mol wt: 418.9579

ACTION – A representative compound from a series of prostaglandin derivatives with prostaglandin D₂ (PGD₂)-like agonist activity, proven to increase cAMP production *in vitro* in bovine fetal trachea-derived cells. Potentially useful in the treatment of nephropathies, as well as cardiovascular disorders such as ischemic cardiopathy, hypertension and heart failure.

SOURCE – Taisho.

REFERENCES

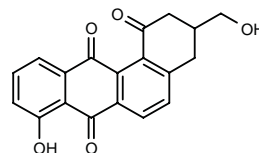
1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin derivs*. WO 0112596.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

301486

8-Hydroxy-3-(hydroxymethyl)-1,2,3,4,7,12-hexahydro-benzo[*a*]anthracene-1,7,12-trione



C19 H14 O5; Mol wt: 322.3146

ACTION – Antiulcer agent isolated from *Streptomyces* sp. Q57219 (FERM P-17283) that acts by virtue of its selective antibacterial activity against *Helicobacter pylori* (MIC = 0.2 μ g/ml); MICs against other bacteria including aerobic and anaerobic microorganisms such as *Staphylococcus aureus* FDA209P, *Escherichia coli* strains and *Pseudomonas aeruginosa* NCTC10490 are > 12.5 μ g/ml.

SOURCE – Yamanouchi.

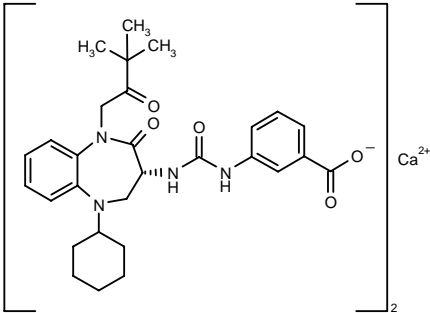
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1. Taniguchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Benzo[a]anthracene-1,7,12-trione derivs*. JP 2001019656.

Z-360

288780

Bis[3-[3-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3(*R*)-yl]ureido]-benzoic acid] calcium salt



C58 H70 Ca N8 O10; Mol wt: 1079.3150

ACTION – Cholecystokinin B (CCK₂) receptor antagonist with higher affinity (K_i = 0.468 nM vs. 11.7 nM) and selectivity (615-fold vs. 39.1-fold) compared to L-365260 for the human CCK₂ receptor over the CCK₁ receptor. Compound inhibited pentagastrin-stimulated acid secretion in rats (ID₅₀ = 0.32 μmol/kg i.d.), where it was more potent than famotidine (ID₅₀ = 1.5 μmol/kg), and dogs (ID₅₀ = 0.76 mg/kg p.o.), but it did not inhibit gastric acid secretion stimulated by histamine or carbachol. In contrast to omeprazole, compound did not induce gastric mucosal hyperplasia following repeated oral doses in rats, but it was able to prevent omeprazole-induced hyperplasia. Moreover, compound was seen to dose-dependently inhibit postprandial acid secretion in rats, with almost complete inhibition at 1 mg/kg i.d., and in Pavlov pouch dogs, where a dose of 30 mg/kg p.o. inhibited postprandial acid secretion by 70%. The compound was comparable to omeprazole and superior to H₂ antagonists in rat models of experimental esophagitis and gastric lesions. Potentially useful for the treatment of gastroesophageal reflux disease (GERD) and peptic ulcers.

SOURCE – Zeria.

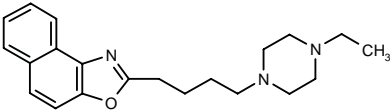
REFERENCES

- Shinozaki, K. et al. (Zeria Pharmaceutical Co., Ltd.) *1,5-Benzodiazepine derivs.* EP 0945445, US 6239131, WO 9825911.
- Miura, N. et al. *Pharmacological profiles of Z-360, a novel CCKB/gastrin (CCK2) receptor antagonist with excellent oral potency.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1605.
- Morita, H. et al. *Effects of Z-360, a novel CCKB/gastrin (CCK2) receptor antagonist, on meal-induced acid secretion and experimental ulcer models in dogs and rats.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1606.
- Zeria updates status of GI pipeline. DailyDrugNews.com (Daily Essentials) 2000, April 25.

AGENTS FOR IRRITABLE BOWEL SYNDROME

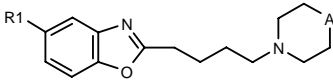
301497

2-[4-(4-Ethylpiperazin-1-yl)butyl]naphtho[1,2-*d*]oxazole



C21 H27 N3 O; Mol wt: 337.4643

ACTION – Agent with affinity for 5-HT₄ receptors (99% inhibition of [³H]-GR113808 binding in guinea pig striatum preparations at 1.0 μM), and potential in the treatment of urinary tract disorders such as dysuria accompanied by urinary tract obstruction or prostatic hypertrophy, as well as CNS disorders such as schizophrenia and depression and gastrointestinal motility disorders such as nausea, vomiting and irritable bowel syndrome. Other exemplified compounds from this series of benzoxazole derivatives include the following:



Compound	R1	A	Formula
301498	H	N(Ph)	C ₂₁ H ₂₅ N ₃ O
301499	Cl	CH2	C ₁₆ H ₂₁ ClN ₂ O
301500	t-Bu	CH2	C ₂₀ H ₃₀ N ₂ O

SOURCE – Meiji Seika.

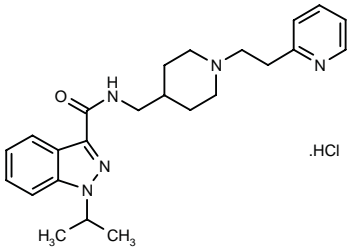
REFERENCES

- Yamamoto, Y. et al. (Meiji Seika Kaisha, Ltd.) *Novel benzoxazole derivs.* JP 2001039957.

AFR-605

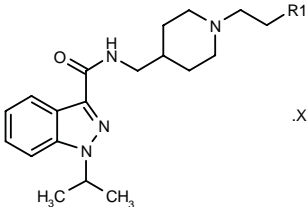
301606

1-Isopropyl-N-[1-[2-(2-pyridyl)ethyl]piperidin-4-ylmethyl]-1*H*-indazole-3-carboxamide hydrochloride



C24 H31 N5 O . HCl; Mol wt: 442.0038

ACTION – 5-HT₄ receptor antagonist, as demonstrated by a pA₂ value of 10.8 against 5-HT-induced relaxation of carbachol-contracted rat esophageal tunica, potentially useful for the treatment of gastrointestinal disorders associated with high intestinal motility such as irritable bowel syndrome, as well as urinary incontinence and cardiac arrhythmias such as atrial fibrillation. Other exemplified compounds from this series of indazole amide derivatives are:



Compound	R1	X	Formula
AFR-603 [301608]	CH2CH2Ph	oxalate	C ₂₇ H ₃₆ N ₄ O ₄
AFR-604 [301611]	cyclohexyl	HCl	C ₂₅ H ₃₆ N ₄ O.HCl
AFR-306 [301612]	Ph	HCl	C ₂₅ H ₃₂ N ₄ O.HCl

SOURCE – ACRAF.

REFERENCES

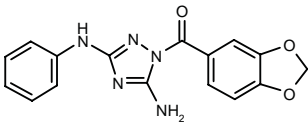
1. Alisi, A. et al. (ACRAF SpA) *Indazole amide cpds. as serotonergic agents*. US 6197769, WO 9303725.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

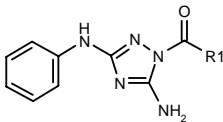
300828

1-(1,3-Benzodioxol-5-ylcarbonyl)-N³-phenyl-1H-1,2,4-triazole-3,5-diamine



C16 H13 N5 O3; Mol wt: 323.3107

ACTION – Potent and selective GSK-3 (glycogen synthase kinase-3) inhibitor, potentially useful for the treatment of diabetes, especially type 2 diabetes, as well as dementias such as Alzheimer’s disease and manic depression. A representative compound from a series of diamino-1,2,4-triazole-carboxylic acid derivatives, wherein the following are also included:



Compound	R1	Formula
300829	(E)-2-furyl-CH=CH	C ₁₅ H ₁₃ N ₅ O ₂
300830	NHPh	C ₁₅ H ₁₄ N ₆ O
300831	cyclohexyl-NH	C ₁₅ H ₂₀ N ₆ O

SOURCE – GlaxoSmithKline.

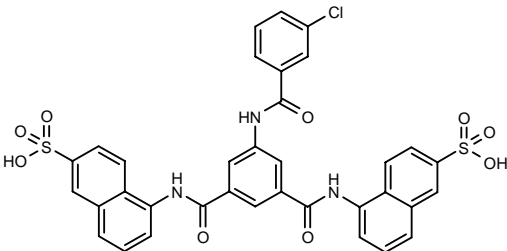
REFERENCES

1. Smith, D.G. and Ward, R.W. (SmithKline Beecham plc) *Diamino-1,2,4-triazole-carboxylic and derivs. as GSK-3 inhibitors*. WO 0109106.

301312

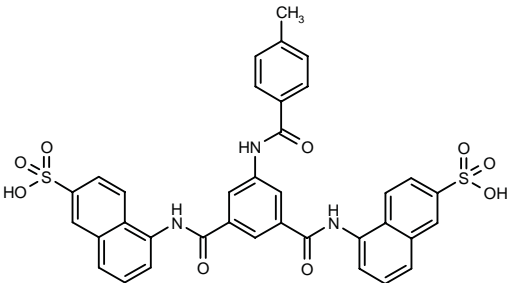
5-[3-(3-Chlorobenzamido)-5-[N-(6-sulfonaphthalen-1-yl)carbamoyl]benzamido]naphthalene-2-sulfonic acid

N-[3,5-Bis[N-(6-sulfonaphthalen-1-yl)carbamoyl]phen-yl]-3-chlorobenzamide



C35 H24 Cl N3 O9 S2; Mol wt: 730.1716

ACTION – Glucose uptake enhancer that stimulates the kinase activity of the insulin receptor and is potentially useful for the treatment of hyperglycemia, particularly type 2 diabetes. This compound increased human insulin receptor phosphorylation by 123.1% in a [³²P]-cytoplasmic kinase domain autophosphorylation assay and enhanced insulin’s ability to effect glucose transport into cultured fibroblast cells (EC₅₀ = 20 μM). It was also reported to lower blood glucose levels in *db/db* mice. Another exemplified compound is:



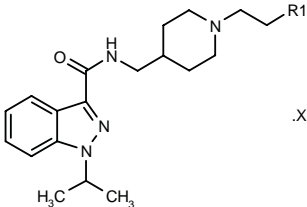
301313: C36 H27 N3 O9 S2

SOURCE – Telik.

REFERENCES

1. Spevak, W.R. et al. (Telik, Inc.) *Novel naphthylsulfonic acids and related cpds. as glucose uptake agonists*. WO 0112591.

ACTION – 5-HT₄ receptor antagonist, as demonstrated by a pA₂ value of 10.8 against 5-HT-induced relaxation of carbachol-contracted rat esophageal tunica, potentially useful for the treatment of gastrointestinal disorders associated with high intestinal motility such as irritable bowel syndrome, as well as urinary incontinence and cardiac arrhythmias such as atrial fibrillation. Other exemplified compounds from this series of indazole amide derivatives are:



Compound	R1	X	Formula
AFR-603 [301608]	CH2CH2Ph	oxalate	C ₂₇ H ₃₆ N ₄ O ₄ ·C ₂ H ₂ O ₄
AFR-604 [301611]	cyclohexyl	HCl	C ₂₅ H ₃₆ N ₄ O·HCl
AFR-306 [301612]	Ph	HCl	C ₂₅ H ₃₂ N ₄ O·HCl

SOURCE – ACRAF.

REFERENCES

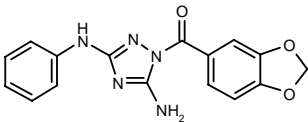
1. Alisi, A. et al. (ACRAF SpA) *Indazole amide cpds. as serotonergic agents*. US 6197769, WO 9303725.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

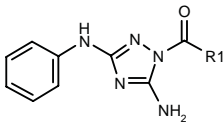
300828

1-(1,3-Benzodioxol-5-ylcarbonyl)-N³-phenyl-1*H*-1,2,4-triazole-3,5-diamine



C16 H13 N5 O3; Mol wt: 323.3107

ACTION – Potent and selective GSK-3 (glycogen synthase kinase-3) inhibitor, potentially useful for the treatment of diabetes, especially type 2 diabetes, as well as dementias such as Alzheimer’s disease and manic depression. A representative compound from a series of diamino-1,2,4-triazole-carboxylic acid derivatives, wherein the following are also included:



Compound	R1	Formula
300829	(E)-2-furyl-CH=CH	C ₁₅ H ₁₃ N ₅ O ₂
300830	NHPh	C ₁₅ H ₁₄ N ₆ O
300831	cyclohexyl-NH	C ₁₅ H ₂₀ N ₆ O

SOURCE – GlaxoSmithKline.

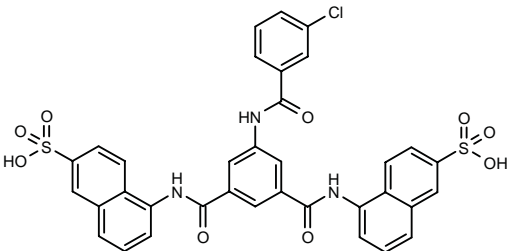
REFERENCES

1. Smith, D.G. and Ward, R.W. (SmithKline Beecham plc) *Diamino-1,2,4-triazole-carboxylic and derivs. as GSK-3 inhibitors*. WO 0109106.

301312

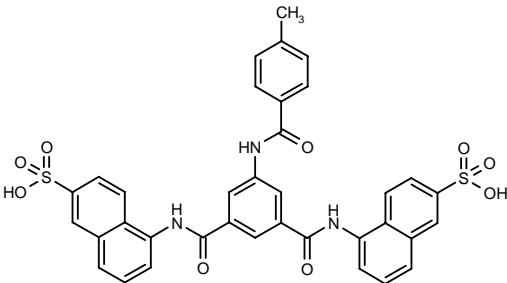
5-[3-(3-Chlorobenzamido)-5-[N-(6-sulfonaphthalen-1-yl)carbamoyl]benzamido]naphthalene-2-sulfonic acid

N-[3,5-Bis[N-(6-sulfonaphthalen-1-yl)carbamoyl]phen-yl]-3-chlorobenzamide



C35 H24 Cl N3 O9 S2; Mol wt: 730.1716

ACTION – Glucose uptake enhancer that stimulates the kinase activity of the insulin receptor and is potentially useful for the treatment of hyperglycemia, particularly type 2 diabetes. This compound increased human insulin receptor phosphorylation by 123.1% in a [³²P]-cytoplasmic kinase domain autophosphorylation assay and enhanced insulin’s ability to effect glucose transport into cultured fibroblast cells (EC₅₀ = 20 μM). It was also reported to lower blood glucose levels in *db/db* mice. Another exemplified compound is:



301313: C36 H27 N3 O9 S2

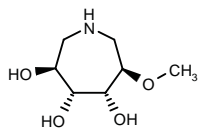
SOURCE – Telik.

REFERENCES

1. Spevak, W.R. et al. (Telik, Inc.) *Novel naphthylsulfonic acids and related cpds. as glucose uptake agonists*. WO 0112591.

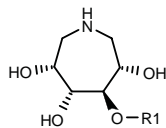
301493

(3*S*,4*R*,5*R*,6*R*)-6-Methoxyperhydroazepine-3,4,5-triol

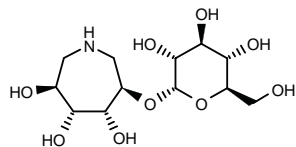


C7 H15 N O4; Mol wt: 177.1985

ACTION – Antidiabetic agent, a selective α -glucosidase inhibitor, as demonstrated *in vitro* by an IC₅₀ value of 0.07 mg/ml against *Bacillus stearotherophilus* α -glucosidase, compared to IC₅₀ values of 9, 4, 6 and 1.5 mg/ml, respectively, against β -glucosidase, α -galactosidase, α -mannosidase and α -fucosidase. Other exemplified compounds from this series of hydroxyazepane derivatives include the following:



Compound	R1	Formula
301494	Me	C ₇ H ₁₅ NO ₄
301495	alpha-D-glucopyranosyl	C ₁₂ H ₂₃ NO ₉



301496: C12 H23 N O9

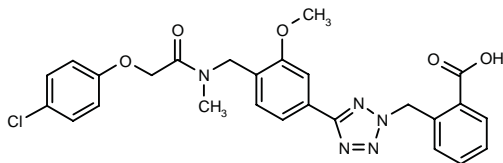
SOURCE – Kikkoman.

REFERENCES

1. Kasai, K. et al. (Kikkoman Corp.) *Hydroxyazepane derivs. and their salts*. JP 2001019675.

301540

2-[5-[4-[*N*-[2-(4-Chlorophenoxy)acetyl]-*N*-methylamino-methyl]-3-methoxyphenyl]-2*H*-tetrazol-2-ylmethyl]benzoic acid



C26 H24 Cl N5 O5; Mol wt: 521.9586

ACTION – A representative compound from a series of benzoic acid derivatives that acts as a peroxisome proliferator activated receptor agonist, particularly PPAR γ receptors and is potentially useful for the treatment of type 2 diabetes mellitus. This compound was tested for its ability to inactivate PPAR isoforms in transfected cells and showed a 64% γ transactivation and a 25% α transactivation at 10 μ M. This compound was found to activate PPAR γ -induced glycerophosphate dehydrogenase activity by 79% in 3T3L1 cells at 10 μ M.

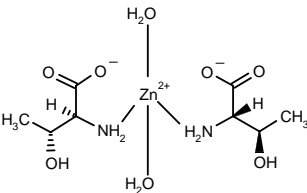
SOURCE – AstraZeneca.

REFERENCES

1. Hargreaves, R.B. and Whittamore, P.R.O. (AstraZeneca plc; AstraZeneca AB) *Benzoic acid derivs. for the treatment of diabetes mellitus*. WO 0112612.

303634

(*OC*-6-22- Δ)-Diaquabis(L-threoninato- κ N, κ O¹)zinc



C8 H20 N2 O8 Zn; Mol wt: 337.6420

ACTION – Insulinomimetic zinc(II) complex proven to inhibit the *in vitro* release of free fatty acids from isolated rat adipocytes (IC₅₀ = 540 μ M) and to significantly lower blood glucose levels in diabetic KKA^y mice. Potentially useful for the treatment of type 2 diabetes.

SOURCES – Kyoto Pharmaceutical University, Kyoto (JP); Japan Science and Technology Corporation; Osaka City University, Osaka (JP); Teikyo University, Utsunomiya (JP).

REFERENCES

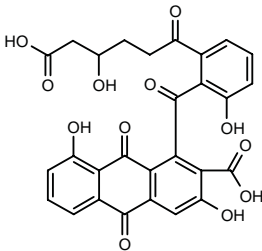
1. Kojima, Y. and Sakurai, H. (Japan Science and Technology Corporation) *Hypoglycemics comprising organic zinc(II) complexes*. JP 2001220348, WO 0139769.

2. Yoshikawa, Y. et al. *New insulinomimetic zinc(II) complexes of α -amino acids and their derivatives with Zn(N2O2) coordination mode*. Chem Pharm Bull 2001, 49(5): 652.

MUMBAISTATIN

303476

1-[2-(5-Carboxy-4-hydroxypentanoyl)-6-hydroxybenzoyl]-3,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid



C28 H20 O12; Mol wt: 548.4540

ACTION – Inhibitor of glucose-6-phosphate translocase (IC₅₀ = 5 nM), isolated from cultures of *Streptomyces* sp. DSM 11641. Potentially useful as a therapy for type 2 diabetes.

SOURCE – Aventis Pharma.

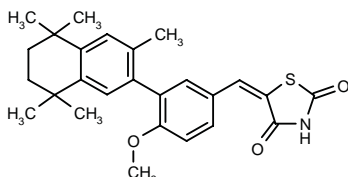
REFERENCES

1. Ramakrishna, N.V.S. et al. (Aventis Pharma Deutschland GmbH) *Mumbaistatin, a process for its production and its use as a pharmaceutical*. WO 9967408.
2. Vertesy, L. et al. *The chemical structure of mumbaistatin, a novel glucose-6-phosphate translocase inhibitor produced by Streptomyces sp. DSM 11641*. J Antibiot 2001, 54(4): 354.

MX-6016^{1,2}

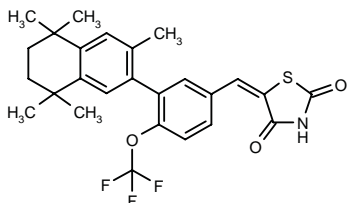
301944

5-[4-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzylidene]thiazolidine-2,4-dione



C26 H29 N O3 S; Mol wt: 435.5851

ACTION – Antidiabetic agent for the treatment of type 2 diabetes, also reported to be useful for the treatment of hyperproliferative disorders such as cancer and inflammatory disorders such as osteoarthritis, rheumatoid arthritis and inflammatory bowel disease. *In vitro*, compound was shown to induce the differentiation of mouse 3T3-L1 preadipocytes into adipocytes both in the absence and presence of insulin. *In vivo*, it was shown to decrease serum glucose and triglyceride levels in *db/db* and *ob/ob* mice at 1 and 5 mg/kg p.o., respectively. Another exemplified compound from this series of benzylidene thiazolidinediones and analogues is:



301945:¹ C26 H26 F3 N O3 S

SOURCE – Maxia.

REFERENCES

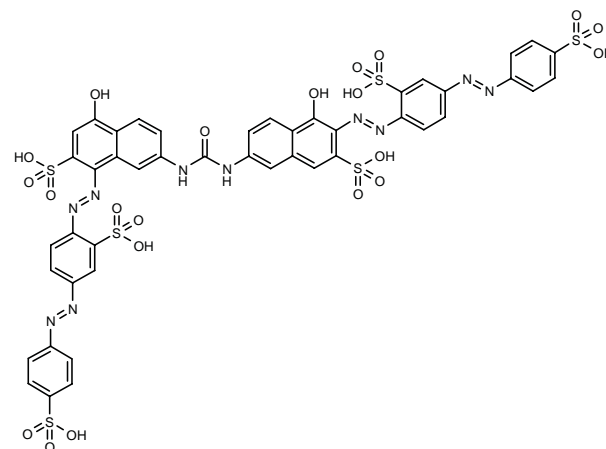
1. Pfahl, M. et al. (Maxia Pharmaceuticals, Inc.) *Benzylidene-thiazolidinediones and analogues and their use in the treatment of diabetes*. WO 0116122.
2. *Company Profile: Maxia Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) 1999, Nov 19.

TLK-16998

256719

4-Hydroxy-7-[3-[5-hydroxy-7-sulfo-6-[2-sulfo-4-(4-sulphophenyldiazenyl)phenyldiazenyl]naphthalen-2-yl]-ureido]-1-[2-sulfo-4-(4-sulphophenyldiazenyl)phenyldiazenyl]naphthalene-2-sulfonic acid

TER-16998



C45 H32 N10 O21 S6; Mol wt: 1241.1930

ACTION – Insulin receptor (IR) sensitizer, a small molecule shown to increase IR auto-phosphorylation in the presence of insulin, as well as downstream signaling events. It activated the tyrosine kinase domain of the IR β subunit at 1 μ mol/l or less, while having little or no effect on insulin binding at up to 100 μ mol/l. Moreover, compound enhanced the insulin-induced phosphorylation of the IR β subunit and insulin receptor substrate-1 and increase in phosphatidylinositol 3-kinase at 3.2 μ mol/l or more, while having no effect itself on IR signaling in murine adipocytes. Compound also enhanced the ability of insulin to stimulate glucose transport in adipocytes at concentrations of 8-40 μ mol/l, while having little or no effect in the absence of insulin or on IGF-1-induced 2-deoxy-D-glucose uptake. In the *db/db* mouse model of type 2 diabetes, compound at a dose of 10 mg/kg i.p. induced a long-lasting reduction (4 h or more) of blood glucose levels (21%) compared to controls. In C57BL/6J mice fed a high-fat diet and subsequently treated with low-dose streptozotocin, another animal model of type 2 diabetes, compound at a dose of 10 mg/kg reduced blood glucose levels by 28% for up to 6 h after dosing. Potentially useful for the treatment of type 2 diabetes.

SOURCES – Sanwa; Telik.

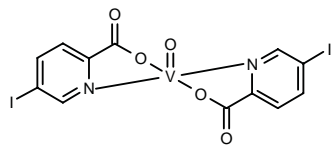
REFERENCES

1. Kauvar, L.M. et al. (Telik, Inc.) *Modulators of insulin receptor activity*. WO 9832017.
2. Mancham, P. et al. *Site of action of TER 16998 - A novel small molecule insulin receptor activator*. Diabetes 2000, 49(Suppl. 1): Abst 1005-P.
3. Mancham, V.P. et al. *A novel small molecule that directly sensitizes the insulin receptor in vitro and in vivo*. Diabetes 2001, 50(4): 824.
4. Sportsman, J.R. *Non-peptide agonists of the insulin receptor*. IBC Pre-Conf Mini-Symp: Nov Ther Approaches Type II Diabetes (March 12, Boston) 1997, 1997.
5. *Telik and Sanwa Kagaku extend drug discovery alliance for second time*. DailyDrugNews.com (Daily Essentials) 2001, Feb 9.

VO(IPA)₂

302577

(*SP-5-21*)-Bis(5-iodopyridine-2-carboxylato-κ*N*¹, κ*O*²)oxovanadium



C12 H6 I2 N2 O5 V; Mol wt: 562.9304

ACTION – Halogenated vanadyl complex with insulin-mimetic activity in rat adipocytes, where it produced concentration-dependent inhibition of epinephrine-induced release of free fatty acids (IC₅₀ = 0.45 mM). *In vivo*, compound was seen to normalize hyperglycemia in streptozotocin-diabetic rats and this normoglycemic effect continued for more than 14 days after the end of treatment. Total vanadium distribution was studied in streptozotocin-diabetic rats treated with the complex for 14 days: the vanadium accumulated especially in bone, kidney, spleen, adipose tissue, liver and pancreas, indicating that the action of vanadium is not peripheral. Moreover, this vanadium complex did not show toxicity during and after 14-day treatment in rats, did not cause thyroid dysfunction and pharmacokinetic studies showed slow elimination of vanadium from the circulation, indicating an association between compound and a blood component such as serum protein or erythrocytes. Potentially useful for the treatment of type 1 diabetes.

SOURCE – Japan Science and Technology.

REFERENCES

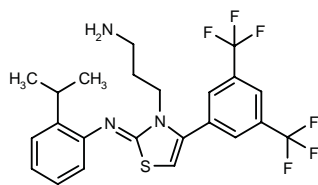
1. Sakurai, H. and Kojima, Y. (Japan Science and Technology Corp.) *Bis (halogenpicolinate) oxovanadium*. JP 2001011083.

2. Takino, T. et al. A new halogenated antidiabetic vanadyl complex bis(5-iodo-picolinato)oxovanadium(IV): *In vitro* and *in vivo* insulinomimetic evaluations and metallokinetic analysis. J Biol Inorg Chem 2001, 6(2): 133.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

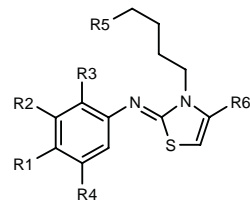
300708

N-[(*Z*)-3-(3-Aminopropyl)-4-[3,5-bis(trifluoromethyl)-phenyl]thiazol-2(3*H*)-ylidene]-*N*-(2-isopropylphenyl)amine

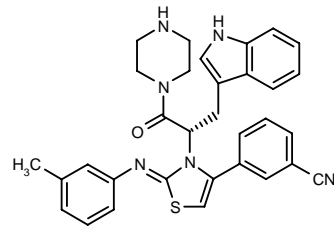


C23 H23 F6 N3 S; Mol wt: 487.5097

ACTION – Somatostatin receptor modulator (K_i < 200 nM), particularly useful for the treatment of acromegaly, hypophysial adenoma and gastroenteropancreatic tumors. Other exemplified 2-arylimino-2,3-dihydrothiazoles are:



Compound	R1	R2	R3	R4	R5	R6	Formula
300709	Cl	H	OMe	OMe	(CH2)2NH2	4-Cl-3-NO2-Ph	C ₂₃ H ₂₆ Cl ₂ N ₄ O ₄ S
300710	H	Me	H	Me	CH2NH2	CONHCH(Ph)2	C ₃₀ H ₃₄ N ₄ OS
300711	H	Me	H	Me	CH2NH2	1-(PhCH2)-4-Pip-NHCO	C ₂₉ H ₃₉ N ₅ OS
300713	H	Me	H	Me	CH2NH2	2,3-(F)2-Ph-CH2NHCO	C ₂₄ H ₂₈ F ₂ N ₄ OS
300714	H	-CH=CH-CH=CH-	H	H	NH2	CONHCH(Ph)2	C ₃₁ H ₃₀ N ₄ OS
300716	H	Me	H	Me	CH2NH2	3,4-Cl-Ph-CH2NHCO	C ₂₄ H ₂₈ Cl ₂ N ₄ OS
300717	H	Me	H	Me	CH2NH2	3-CF3-Ph-CH2NHCO	C ₂₅ H ₂₉ F ₃ N ₄ OS
300719	H	Me	H	Me	CH2NH2	CONH-CH(Me)Ph	C ₂₅ H ₃₂ N ₄ OS



300720: C32 H30 N6 O S

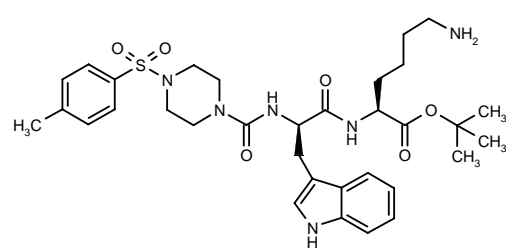
SOURCE – SCRAS.

REFERENCES

1. Moinet, C. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) 2-Arylimino-2,3-dihydrothiazoles, and their use thereof as somatostatin receptor ligands. FR 2796643, WO 0107424.

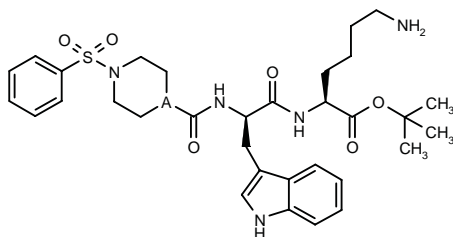
301880

N-[4-(4-Methylphenylsulfonyl)piperazin-1-ylcarbonyl]-*D*-tryptophyl-L-lysine *tert*-butyl ester



C33 H46 N6 O6 S; Mol wt: 654.8284

ACTION – Somatostatin sst₂ receptor antagonist that increases growth hormone (GH) secretion and is thus potentially useful for the treatment of GH deficiency and diseases characterized by decreased levels of GH, glucagon or gastrin such as frailty, hypoglycemia, wrinkled skin, slow skeletal growth, reduced immune function, reduced organ function, fertility disorders, bone disorders, AIDS-related complex, cachexia, cardiac failure, ischemic heart disease, colon disease, metabolic disorders, renal failure, muscular dystrophy and Turner's syndrome. Other exemplified compounds from this series of piperidine and piperazine derivatives include the following:



Compound	A	Formula
301881	CH	C ₃₃ H ₄₅ N ₅ O ₆ S
301882	N	C ₃₂ H ₄₄ N ₆ O ₆ S

SOURCE – Pfizer.

REFERENCES

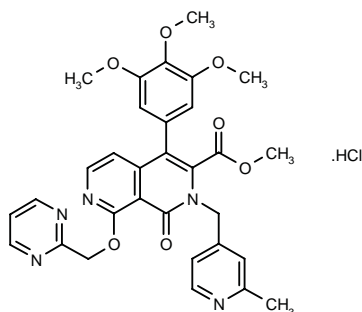
1. Hay, B.A. et al. (Pfizer Products Inc.) *Somatostatin antagonists and agonists that act at the SST subtype 2 receptor*. EP 1086947, JP 2001114761.

TREATMENT OF MALE SEXUAL DYSFUNCTION

T-0156*

287229

2-(2-Methylpyridin-4-ylmethyl)-1-oxo-8-(2-pyrimidinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro[2,7]-naphthyridine-3-carboxylic acid methyl ester hydrochloride



C31 H29 N5 O7 . HCl; Mol wt: 620.0590

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 0.233 nM) with > 40,000-fold selectivity over PDE1, PDE2, PDE3 and PDE4 and superior activity than sildenafil against PDE5. Compound was also more potent than sildenafil in potentiating penile tumescence induced by pelvic nerve stimulation in anesthetized dogs, with efficacy at doses of 0.003-0.3 mg/kg i.v. and 0.3-1 mg/kg i.d. In contrast, it was less active than sildenafil against PDE6, both *in vitro* (IC₅₀ = 0.056 μM vs. 0.028 μM) and *in vivo*. Potentially useful for the treatment of erectile dysfunction.

SOURCE – Tanabe Seiyaku.

REFERENCES

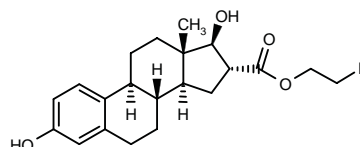
1. Ukita, T. et al. (Tanabe Seiyaku Co., Ltd.) *Naphthyridine derivs. and process for the preparation thereof*. JP 2001031679, WO 0012503.
2. Kikkawa, K. et al. *Pharmacological profile of T-0156, a newly synthesized phosphodiesterase type 5 inhibitor, in anesthetized dogs*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-891.
3. Nakamura, K. et al. *Synthesis and pharmacological activity of naphthyridinone derivatives with specific PDE5 inhibitory effects*. 121st Annu Meet Pharm Soc Jpn (March 28-30, Hokkaido) 2001, Abst 29(PB)I-049.

*Identified compound **287229** (see **287227**) Drug Data Rep 2000, 022(06): 0509.

TREATMENT OF GYNECOLOGICAL DISORDERS

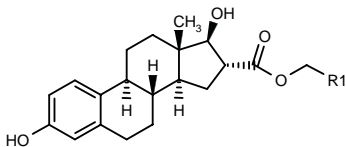
303832

(16α,17β)-3,17-Dihydroxyestra-1(10),2,4-triene-16-carboxylic acid 2-fluoroethyl ester



C21 H27 F O4; Mol wt: 362.4383

ACTION – Estradiol analogue with high estrogen receptor binding affinity and estrogenic potency in an *in vitro* assay in human endometrial adenocarcinoma Ishikawa cells, as well as *in vivo* in rat uterus. Due to its rapid *in vivo* hydrolysis, compound showed high vaginal activity and low systemic activity. It inhibited vaginal reductase activity in castrated female mice following a single intravaginal dose, while displaying very low systemic activity in the uterotrophic assay in immature female rats. Potentially useful for the treatment of women with vaginal dyspareunia, a frequent symptom of the meno-pause. Within this series of estradiol 16α-carboxylic acid esters, the following are also described:



Compound	R1	Formula
303833	H	C ₂₀ H ₂₆ O ₄
303834	Me	C ₂₁ H ₂₈ O ₄

SOURCE – Yale University, New Haven, CT (US).

REFERENCES

1. Labaree, D.C. et al. *Estradiol-16 α -carboxylic acid esters as locally active estrogens.* J Med Chem 2001, 44(11): 1802.

AGENTS FOR FEMALE INFERTILITY

LUTROPIN ALFA

Prop INN

230542

Luteinizing hormone (human α -subunit reduced complex with human β -subunit reduced), glycoform α . α -subunit: chorionic gonadotropin (human α -subunit protein moiety reduced); β -subunit: luteinizing hormone (human β -subunit protein moiety reduced)

Recombinant human luteinizing hormone⁺
rhLH

ACTION – Recombinant human luteinizing hormone.

INDICATION – Treatment of women with an endocrine form of infertility characterized by severe luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency.

PRESENTATION – Powder, 75 IU, and solvent for solution for s.c. injection.

PROPRIETARY NAME – Luveris (IT).

SOURCE – Serono.

REFERENCES

1. Baird, D.T. et al. *Recent development in gonadotrophins for clinical therapy.* J Endocrinol 1996, 148(Suppl.): Abst S38.

2. Cortvrindt, R. et al. *Recombinant luteinizing hormone as a survival and differentiation factor increases oocyte maturation in recombinant follicle stimulating hormone-supplemented mouse preantral follicle culture.* Hum Reprod 1998, 13(5): 1292.

3. Engrand, P. et al. *Recombinant human luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: Results of a multicenter double-blind study.* J Clin Endocrinol Metab 2001, 86(6): 2607.

4. Hakola, K. et al. *Recombinant forms of rat and human luteinizing hormone and follicle-stimulating hormone; comparison of functions in vitro and in vivo.* J Endocrinol 1998, 158(3): 441.

5. le Cotonnec, J.-Y. et al. *Clinical pharmacology of recombinant human luteinizing hormone: Part I. Pharmacokinetics after intravenous administration to healthy female volunteers and comparison with urinary human luteinizing hormone.* Fertil Steril 1998, 69(2): 189.

6. le Cotonnec, J.-Y. et al. *Clinical pharmacology of recombinant human luteinizing hormone: Part II. Bioavailability of recombinant human luteinizing hormone assessed with an immunoassay and an in vitro bioassay.* Fertil Steril 1998, 69(2): 195.

7. le Cotonnec, J.Y. et al. *Pharmacokinetic and pharmacodynamic interactions between recombinant human luteinizing hormone and recombinant human follicle stimulating hormone.* Fertil Steril 1998, 69(2): 201.

8. Loumaye, E. et al. *Results of a phase II, dose-finding, clinical study comparing recombinant human luteinizing hormone (r-hLH) with human chorionic gonadotrophin (hCG) to induce final follicular maturation prior to in vitro fertilization.* Fertil Steril 1998, 70(3, Suppl. 1): Abst O-236.

9. Robert, P. et al. *Immunochemical mapping of human lutropin: I. Delineation of a conformational antigenic determinant.* Mol Cell Endocrinol 1994, 101(1-2): 11.

10. Werlin, L. et al. *A multi-center, randomized, comparative, open-label trial to assess the safety and efficacy of Gonal-F (r-hFSH) versus Gonal-F and recombinant human lutenizing hormone (r-hLH) in patients undergoing ICSI: Preliminary data.* Fertil Steril 1999, 72(3, Suppl. 1): Abst O-032.

11. Williams, R.S. et al. *A multi-center study comparing the efficacy of recombinant human follicle stimulating hormone (r-hFSH, Gonal-F®) versus r-hFSH plus recombinant human luteinizing hormone (r-hLH, Lhad®) in patients undergoing controlled ovarian hyperstimulation (COH) for assisted reproductive technologies (ART).* Fertil Steril 2000, 74(3, Suppl. 1): Abst P-428.

12. Young, I. et al. *Effects of human recombinant LH and FSH in patients with acquired hypogonadotropic hypogonadism: Study of Sertoli and Leydig cell secretions and interactions.* 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-373.

13. *Ares-Serono files for approval of new infertility treatment.* DailyDrugNews.com (Daily Essentials) 1999, Oct 7.

14. *Ares-Serono: Annual Report 1998.* DailyDrugNews.com (Daily Essentials) 1999, May 18.

15. *CPMP recommends marketing approval for Serono's new treatment of female infertility.* DailyDrugNews.com (Daily Essentials) 2000, Aug 17.

16. *Luveris reaches first market following late November approval by European Commission.* DailyDrugNews.com (Daily Essentials) 2001, June 1.

17. *Major advances in infertility treatment announced by Serono.* DailyDrugNews.com (Daily Essentials) 2001, Jan 5.

18. *Proposed international nonproprietary names: List No. 71.* WHO Drug Inf 1994, 8(2): 100.

19. *The Ares-Serono Group and Organon conclude settlement agreement.* Ares-Serono Group Press Release 1995, May 23.

20. Ares-Serono Group Annual Report 1994.

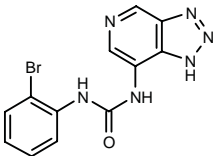
⁺Drug Data Rep 1998, 020(06): 0513.

DERMATOLOGIC DRUGS

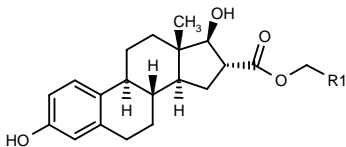
ANTIPSORIATICS

300705

1-(2-Bromophenyl)-3-(1*H*-[1,2,3]triazolo[4,5-*c*]pyridin-7-yl)urea



C12 H9 Br N6 O; Mol wt: 333.1481



Compound	R1	Formula
303833	H	C ₂₀ H ₂₆ O ₄
303834	Me	C ₂₁ H ₂₈ O ₄

SOURCE – Yale University, New Haven, CT (US).

REFERENCES

1. Labaree, D.C. et al. *Estradiol-16 α -carboxylic acid esters as locally active estrogens.* J Med Chem 2001, 44(11): 1802.

AGENTS FOR FEMALE INFERTILITY

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Recombinant human luteinizing hormone⁺
rhLH

ACTION – Recombinant human luteinizing hormone.

INDICATION – Treatment of women with an endocrine form of infertility characterized by severe luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency.

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PROPRIETARY NAME – Luveris (IT).

SOURCE – Serono.

REFERENCES

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2. Cortvrindt, R. et al. *Recombinant luteinizing hormone as a survival and differentiation factor increases oocyte maturation in recombinant follicle stimulating hormone-supplemented mouse preantral follicle culture.* Hum Reprod 1998, 13(5): 1292.

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6. le Cotonnec, J.-Y. et al. *Clinical pharmacology of recombinant human luteinizing hormone: Part II. Bioavailability of recombinant human luteinizing hormone assessed with an immunoassay and an in vitro bioassay.* Fertil Steril 1998, 69(2): 195.

7. le Cotonnec, J.Y. et al. *Pharmacokinetic and pharmacodynamic interactions between recombinant human luteinizing hormone and recombinant human follicle stimulating hormone.* Fertil Steril 1998, 69(2): 201.

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9. Robert, P. et al. *Immunochemical mapping of human lutropin: I. Delineation of a conformational antigenic determinant.* Mol Cell Endocrinol 1994, 101(1-2): 11.

10. Werlin, L. et al. *A multi-center, randomized, comparative, open-label trial to assess the safety and efficacy of Gonal-F (r-hFSH) versus Gonal-F and recombinant human luteinizing hormone (r-hLH) in patients undergoing ICSI: Preliminary data.* Fertil Steril 1999, 72(3, Suppl. 1): Abst O-032.

11. Williams, R.S. et al. *A multi-center study comparing the efficacy of recombinant human follicle stimulating hormone (r-hFSH, Gonal-F®) versus r-hFSH plus recombinant human luteinizing hormone (r-hLH, Lhad®) in patients undergoing controlled ovarian hyperstimulation (COH) for assisted reproductive technologies (ART).* Fertil Steril 2000, 74(3, Suppl. 1): Abst P-428.

12. Young, I. et al. *Effects of human recombinant LH and FSH in patients with acquired hypogonadotropic hypogonadism: Study of Sertoli and Leydig cell secretions and interactions.* 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-373.

13. *Ares-Serono files for approval of new infertility treatment.* DailyDrugNews.com (Daily Essentials) 1999, Oct 7.

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19. *The Ares-Serono Group and Organon conclude settlement agreement.* Ares-Serono Group Press Release 1995, May 23.

20. Ares-Serono Group Annual Report 1994.

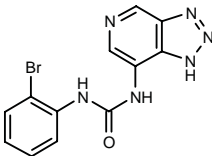
⁺Drug Data Rep 1998, 020(06): 0513.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

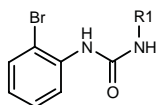
300705

1-(2-Bromophenyl)-3-(1*H*-[1,2,3]triazolo[4,5-*c*]pyridin-7-yl)urea



C12 H9 Br N6 O; Mol wt: 333.1481

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist that is expected to be useful in the treatment of disorders characterized by excessive or unregulated IL-8 including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, cardiac and renal reperfusion injury, glomerulo-nephritis, thrombosis, graft-vs.-host disease, Alzheimer's disease, allograft rejection, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cell release. Other exemplified cyclic pyridyl substituted compounds are:



Compound	R1	Formula
300706	1H-1,2,3-triazolo[4,5-b]pyridin-7-yl	C ₁₂ H ₉ BrN ₆ O
300707	1H-1,2,3-triazolo[4,5-c]pyridin-4-yl	C ₁₂ H ₉ BrN ₆ O

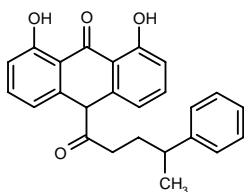
SOURCE – GlaxoSmithKline.

REFERENCES

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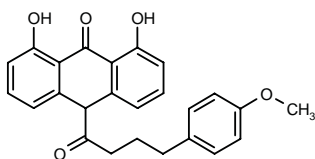
303463

1,8-Dihydroxy-10-(4-phenylpentanoyl)anthracen-9(10*H*)-one



C₂₅ H₂₂ O₄; Mol wt: 386.4448

ACTION – LTB₄ biosynthesis inhibitor (IC₅₀ = 0.3 μM in bovine polymorphonuclear cells) with antiproliferative activity against HaCaT cells (IC₅₀ = 0.8 μM) comparable to that of the antipsoriatic anthralin (IC₅₀ = 0.7 μM). In contrast to anthralin, both cytotoxic effect against cell membranes and hydroxyl radical formation were strongly reduced. Potentially useful as an antipsoriatic agent. Another related compound within this series of 10-phenylbutyryl-substituted anthracenones, is:



303462: C₂₅ H₂₂ O₅

SOURCE – Teva.

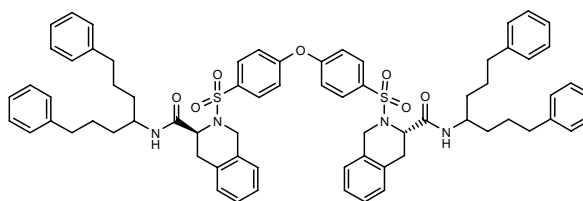
REFERENCES

1. Muller, K. et al. (Teva Pharmaceutical Industries Ltd.) *10-Substd. 18-dihydroxy-9(10H)anthracenone pharmaceuticals*. US 5952390.
2. Müller, K. et al. *10-Phenylbutyryl-substituted anthracenones as inhibitors of keratinocyte growth and LT_{B4} biosynthesis*. Eur J Med Chem 2001, 36(2): 179.

HAIR GROWTH STIMULANTS

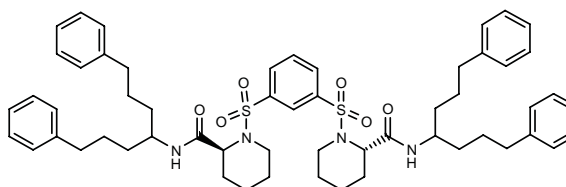
301143

2,2'-Oxybis(1,4-phenylene)bis(sulfonyl)bis[*N*-[4-phenyl-1-(3-phenylpropyl)butyl]-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxamide]



C₇₀ H₇₄ N₄ O₇ S₂; Mol wt: 1147.5080

ACTION – Agent for the treatment of hair loss including arresting and/or reversing hair loss and promoting hair growth, which may also be useful for the treatment of multidrug resistance, AIDS, cardiac injury and neurological disorders. Another exemplified multivalent sulfonamide is:



301145: C₅₆ H₇₀ N₄ O₆ S₂

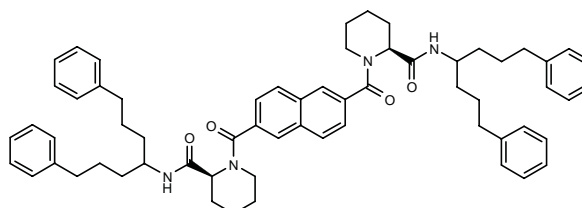
SOURCE – Procter & Gamble.

REFERENCES

1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *Multivalent sulfonamides*. WO 0110837.

301146

1,1'-(Naphthalene-2,6-diyl)bis(carbonyl)bis[*N*-[4-phenyl-1-(3-phenylpropyl)butyl]piperidine-2(*S*)-carboxamide]



C₆₂ H₇₂ N₄ O₄; Mol wt: 937.2748

ACTION – A representative compound from a series of multivalent ketoamides and amides that is useful for the treatment of hair loss including arresting and/or reversing hair loss and promoting hair growth. It may also be useful for the treatment of multidrug resistance, AIDS, cardiac injury and neurological disorders.

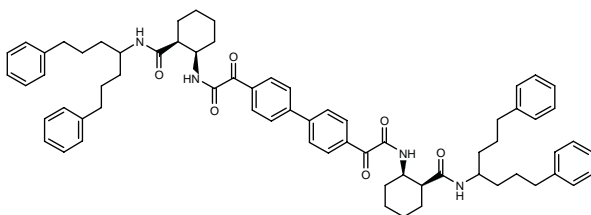
SOURCE – Procter & Gamble.

REFERENCES

1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *Method of treating hair loss using multivalent ketoamides and amides*. WO 0110836.

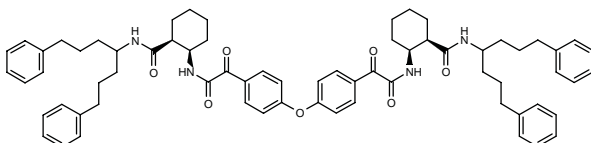
301147

2(*R*),2'(*R*)-(Biphenyl-4,4'-diyl)bis(1,2-dioxoethylene)-bis(imino)bis[*N*-[4-phenyl-1-(3-phenylpropyl)butyl]-cyclohexane-1(*S*)-carboxamide]



C68 H78 N4 O6; Mol wt: 1047.3860

ACTION – Agent for the treatment of hair loss including arresting and/or reversing hair loss and promoting hair growth, which may also be useful for the treatment of multidrug resistance, AIDS, cardiac injury and neurological disorders. Another exemplified multivalent exocyclic diketo compound is:



301148: C68 H78 N4 O7

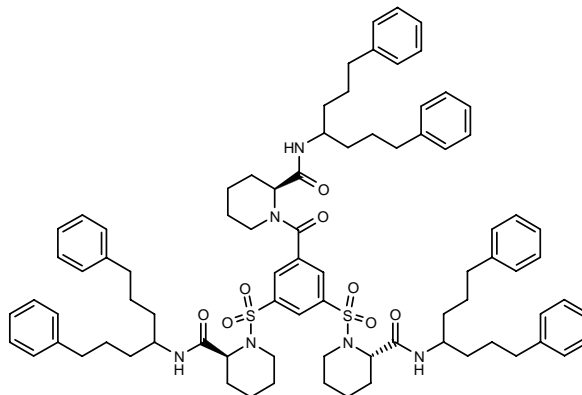
SOURCE – Procter & Gamble.

REFERENCES

1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *Multivalent exocyclic diketo cpds*. WO 0110821.

301149

1-[3,5-Bis[2(*S*)-[*N*-[4-phenyl-1-(3-phenylpropyl)butyl]-carbamoyl]piperidin-1-ylsulfonyl]benzoyl]-*N*-[4-phenyl-1-(3-phenylpropyl)butyl]piperidine-2(*S*)-carboxamide



C82 H102 N6 O8 S2; Mol wt: 1363.8740

ACTION – A representative compound from a series of multivalent compounds that is useful for the treatment of hair loss including arresting and/or reversing hair loss and promoting hair growth. It may also be useful for the treatment of multidrug resistance, AIDS, cardiac injury and neurological disorders.

SOURCE – Procter & Gamble.

REFERENCES

1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *Multivalent cpds*. WO 0110838.

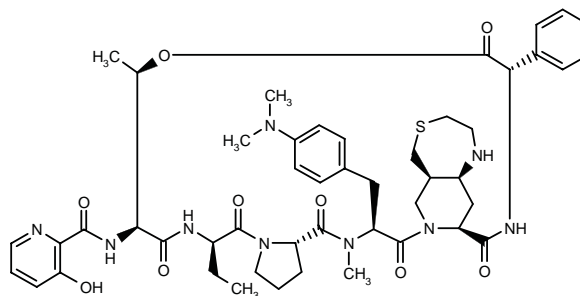
ANTIINFECTIVE THERAPY

ANTIBIOTICS

300744

5-[(5a*R*,8*S*,9a*S*)-Decahydropyrido[4,3-*e*][1,4]thiazepine-8-carboxylic acid]pristinamycin 1A

N-(3-Hydroxypyridin-2-ylcarbonyl)-*L*-threonyl-*D*-(2-aminobutyl)-*L*-prolyl-*L*-*N*-methyl-[4-(*N,N*-dimethylamino)]phenylalanyl-*L*-[(5a*R*,8*S*,9a*S*)-octahydropyrido[4,3-*e*][1,4]thiazepin-7,8(5*H*)-ylcarbonyl]-*L*-phenylglycine C-1.6-*O*-3.1-lactone



C48 H61 N9 O9 S; Mol wt: 940.1299

ACTION – A representative compound from a series of multivalent ketoamides and amides that is useful for the treatment of hair loss including arresting and/or reversing hair loss and promoting hair growth. It may also be useful for the treatment of multidrug resistance, AIDS, cardiac injury and neurological disorders.

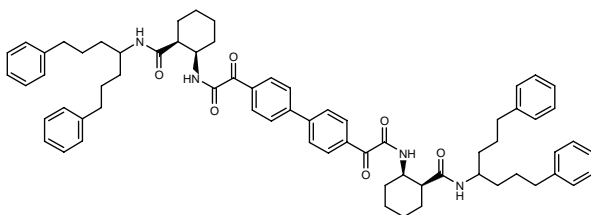
SOURCE – Procter & Gamble.

REFERENCES

1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *Method of treating hair loss using multivalent ketoamides and amides*. WO 0110836.

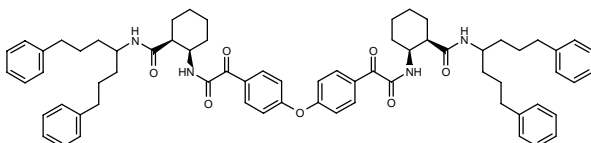
301147

2(*R*),2'(*R*)-(Biphenyl-4,4'-diyl)bis(1,2-dioxoethylene)-bis(imino)bis[*N*-[4-phenyl-1-(3-phenylpropyl)butyl]-cyclohexane-1(*S*)-carboxamide]



C68 H78 N4 O6; Mol wt: 1047.3860

ACTION – Agent for the treatment of hair loss including arresting and/or reversing hair loss and promoting hair growth, which may also be useful for the treatment of multidrug resistance, AIDS, cardiac injury and neurological disorders. Another exemplified multivalent exocyclic diketo compound is:



301148: C68 H78 N4 O7

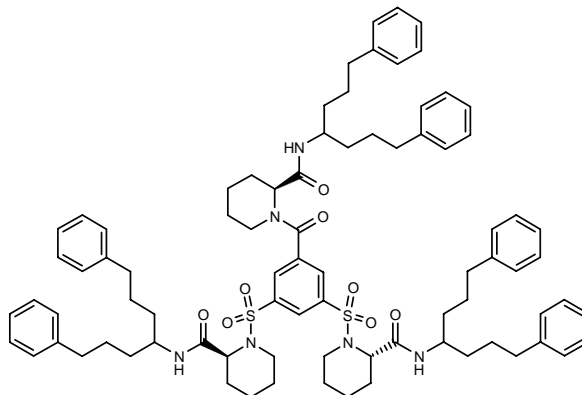
SOURCE – Procter & Gamble.

REFERENCES

1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *Multivalent exocyclic diketo cpds*. WO 0110821.

301149

1-[3,5-Bis[2(*S*)-[*N*-[4-phenyl-1-(3-phenylpropyl)butyl]-carbamoyl]piperidin-1-ylsulfonyl]benzoyl]-*N*-[4-phenyl-1-(3-phenylpropyl)butyl]piperidine-2(*S*)-carboxamide



C82 H102 N6 O8 S2; Mol wt: 1363.8740

ACTION – A representative compound from a series of multivalent compounds that is useful for the treatment of hair loss including arresting and/or reversing hair loss and promoting hair growth. It may also be useful for the treatment of multidrug resistance, AIDS, cardiac injury and neurological disorders.

SOURCE – Procter & Gamble.

REFERENCES

1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *Multivalent cpds*. WO 0110838.

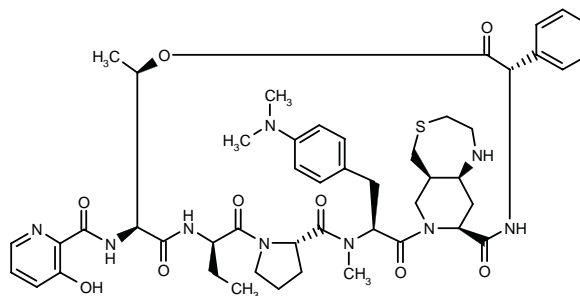
ANTIINFECTIVE THERAPY

ANTIBIOTICS

300744

5-[(5a*R*,8*S*,9a*S*)-Decahydropyrido[4,3-*e*][1,4]thiazepine-8-carboxylic acid]pristinamycin 1A

N-(3-Hydroxypyridin-2-ylcarbonyl)-*L*-threonyl-*D*-(2-aminobutyl)-*L*-prolyl-*L*-*N*-methyl-[4-(*N,N*-dimethylamino)]phenylalanyl-*L*-[(5a*R*,8*S*,9a*S*)-octahydropyrido[4,3-*e*][1,4]thiazepin-7,8(5*H*)-ylcarbonyl]-*L*-phenylglycine C-1.6-*O*-3.1-lactone



C48 H61 N9 O9 S; Mol wt: 940.1299

ACTION – A semisynthetic derivative of streptogramin B that is useful as an antimicrobial agent alone or in combination with a streptogramin A derivative.

SOURCE – Aventis Pharma.

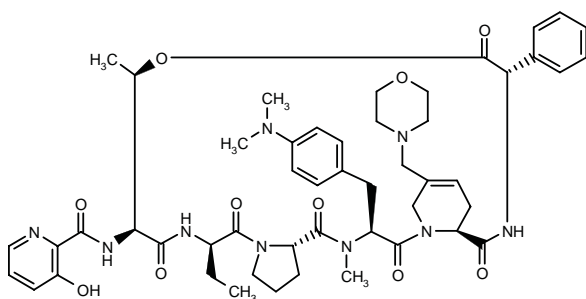
REFERENCES

1. Bacque, E. et al. (Aventis Pharma SA) *Streptogramin derivs., preparation and compsns. containing same*. FR 2796950, WO 0107467.

301114

5-[(2*S*)-1,2,3,4-Tetrahydro-5-(4-morpholinylmethyl)-2-pyridinecarboxylic acid]pristinamycin 1A

N-(3-Hydroxypyridin-2-ylcarbonyl)-*L*-threonyl-*D*-(2-aminobutyl)-*L*-prolyl-*L*-*N*-methyl-[4-(*N,N*-dimethyl-amino)]phenylalanyl-*L*-[5-(morpholin-4-ylmethyl)-1,2,3,6-tetrahydropyridin-2(*S*)-ylcarbonyl]-2-phenyl-*L*-glycine C-1.6-*O*-3.1-lactone



C50 H63 N9 O10; Mol wt: 950.1007

ACTION – A representative compound from a series of streptogramin B derivatives that is expected to be useful as an antimicrobial agent, preferably in combination with at least one streptogramin A derivative.

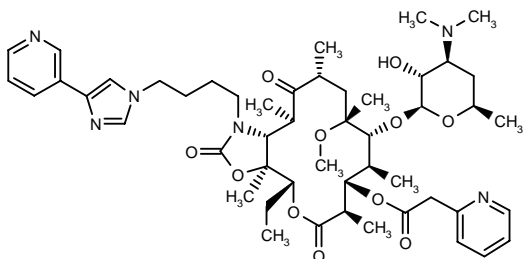
SOURCE – Aventis Pharma.

REFERENCES

1. Bacqué, E. et al. (Aventis Pharma SA) *Streptogramin derivs., production thereof and compsns. containing the same*. FR 2796949, WO 0110895.

301270

11-Deoxy-3-*O*-des(hexopyranosyl)-3-*O*-[2-(2-pyridyl)acetyl]-6-*O*-methyl-11-[4-[4-(3-pyridyl)-1*H*-imidazol-1-yl]butylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C50 H72 N6 O11; Mol wt: 933.1498

ACTION – Antibacterial agent, an erythromycin A derivative with potent antimicrobial activity against erythromycin-resistant bacteria and *Haemophilus influenzae*. *In vitro*, compound gave MIC values of 0.10, 0.20, 0.05, 0.10 and 0.39 µg/ml, respectively, against *Staphylococcus aureus* 209P-JC and B1 and *Streptococcus pneumoniae* IID553, 210 and 205, being more potent than clarithromycin (MIC = 0.10, > 100, 0.10, 0.78 and > 100 µg/ml, respectively) and azithromycin (MIC = 0.20, > 100, 0.20, 1.56 and > 100 µg/ml, respectively).

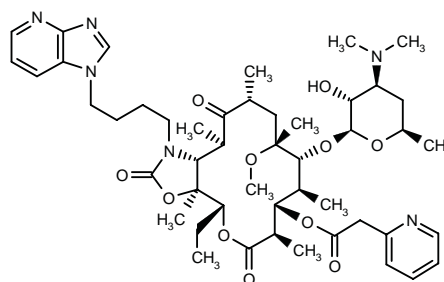
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A derivs.* WO 0110879.

301272

11-Deoxy-3-*O*-des(hexopyranosyl)-3-*O*-[2-(2-pyridyl)acetyl]-6-*O*-methyl-11-[4-(1*H*-imidazo[4,5-*b*]pyridin-1-yl)butylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C48 H70 N6 O11; Mol wt: 907.1120

ACTION – Antibacterial agent, an erythromycin A derivative with potent antimicrobial activity against erythromycin-resistant bacteria and *Haemophilus influenzae*. *In vitro*, compound gave MIC values of 0.05, 0.20, 0.10, 0.20 and 0.39 µg/ml, respectively, against *Staphylococcus aureus* 209P-JC and B1 and *Streptococcus pneumoniae* IID553, 210 and 205, being more potent than clarithromycin (MIC = 0.10, > 100, 0.10, 0.78 and > 100 µg/ml, respectively) and azithromycin (MIC = 0.20, > 100, 0.20, 1.56 and > 100 µg/ml, respectively).

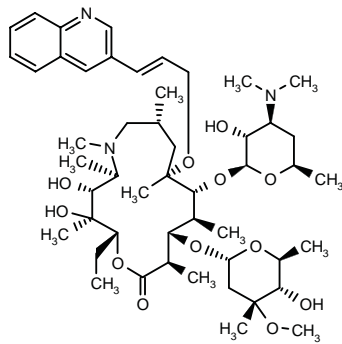
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A derivs.* WO 0110880.

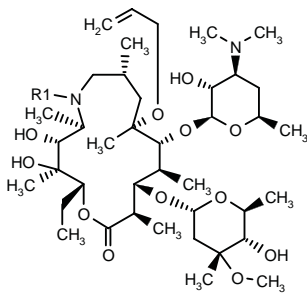
301707

9-Deoxo-9a-methyl-6- *O*-[3-(3-quinolinyl)-2-propenyl]-9a-aza-9a-homoerythromycin A

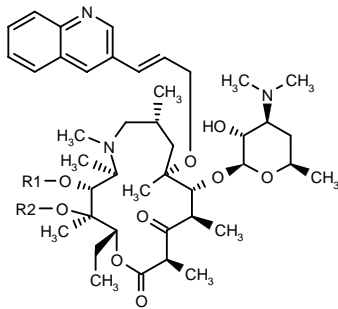


C50 H81 N3 O12; Mol wt: 916.1989

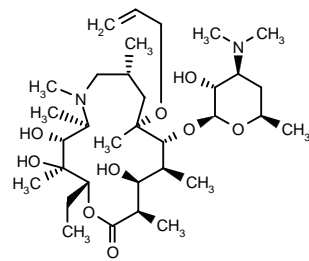
ACTION – Antibacterial agent active against Gram-positive bacteria and some Gram-negative pathogens, as demonstrated *in vitro* by MIC values of 0.1, 0.2, 0.05, 0.2, 0.39, 0.05 and 0.12 µg/ml, respectively, against *Staphylococcus aureus* ATCC6538P, *Staphylococcus epidermidis* 3519, *Streptococcus pyogenes* EES61, *Micrococcus luteus* ATCC4698, *Escherichia coli* SS, *Nocardia asteroides* ATCC99700 and *Streptococcus pneumoniae* ATCC6303, compared to MIC values of 0.2, 0.39, 0.05, 0.2, 0.78, 0.1 and 0.06 µg/ml, respectively, for erythromycin A. Other exemplified compounds from this series of 9a-azalides include the following:



Compound	R1	Formula
301708	H	C ₄₀ H ₇₄ N ₂ O ₁₂
301712	Me	C ₄₁ H ₇₆ N ₂ O ₁₂



Compound	R1	R2	Formula
301714	H	H	C ₄₂ H ₈₅ N ₃ O ₉
301715	-CO-		C ₄₃ H ₈₃ N ₃ O ₁₀



301713: C33 H62 N2 O9

SOURCE – Abbott.

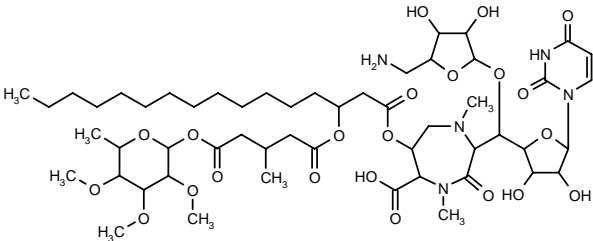
REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) 9A-Azalides with antibacterial activity. WO 0114397.

CAPRAZAMYCIN A

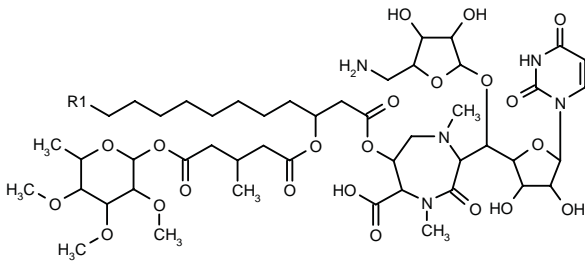
301898

2-[1-[5-(Aminomethyl)-3,4-dihydroxytetrahydrofuran-2-yloxy]-1-[5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-3,4-dihydroxytetrahydrofuran-2-yl]methyl]-1,4-dimethyl-6-[3-[3-methyl-5-oxo-5-(3,4,5-trimethoxy-6-methyl-tetrahydropyran-2-yloxy)pentanoyloxy]hexadecanoyloxy]-3-oxohexahydro-1,4-diazepine-5-carboxylic acid



C53 H87 N5 O22; Mol wt: 1146.2830

ACTION – Antibacterial agent isolated from a culture of *Streptomyces* sp. MK730-62F2 (FERM BP-7218) with good activity against mycobacteria and bacteria. *In vitro*, compound gave MIC values of 0.78-1.56 µg/ml against a variety of antibiotic-resistant *Mycobacterium smegmatis* ATCC607 strains, as well as MIC values of 1.56 and 6.25 µg/ml against *Mycobacterium phlei* and *Mycobacterium fortuitum*, respectively. Other compounds isolated from the same source are:



Compound	R1	Formula
Caprazamycin B [301899]	i-BuCH2	C ₅₃ H ₈₇ N ₅ O ₂₂
Caprazamycin C [301900]	Bu	C ₅₂ H ₈₆ N ₅ O ₂₂
Caprazamycin E [301901]	Pr	C ₅₁ H ₈₃ N ₅ O ₂₂
Caprazamycin F [301902]	i-Pr	C ₅₁ H ₈₃ N ₅ O ₂₂

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

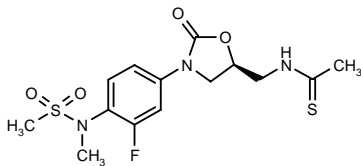
REFERENCES

1. Takeuchi, T. et al. (Microbial Chemistry Research Foundation) *Antibiotic caprazamycins and process for producing the same*. WO 0112643.

ANTIBACTERIAL DRUGS

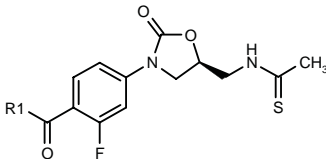
300835

N-[3-[3-Fluoro-4-[*N*-methyl-*N*-(methylsulfonyl)amino]-phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]thioacetamide



C14 H18 F N3 O4 S2; Mol wt: 375.4432

ACTION – Oxazolidinone antibacterial agent active against Gram-positive and Gram-negative aerobic and anaerobic bacteria such as staphylococci (MIC = 4-8 µg/ml against *Staphylococcus aureus*), enterococci, streptococci, *Haemophilus*, *Moraxella* and *Escherichia*. Other specifically claimed compounds from this series of oxazolidinone derivatives include the following:



Compound	R1	Formula
300836	2-imidazolyl-NH	C ₁₆ H ₁₆ FN ₅ O ₃ S
300837	OMe	C ₁₄ H ₁₅ FN ₂ O ₄ S
300838	6-Cl-3-Pyr-NH	C ₁₈ H ₁₆ ClFN ₄ O ₃ S
300839	2-thiazolyl-NH	C ₁₆ H ₁₅ FN ₄ O ₃ S ₂

SOURCE – Pharmacia.

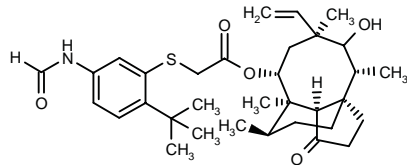
REFERENCES

1. Gordeev, M.F. et al. (Pharmacia Corp.) *Oxazolidinones and their use as anti-infectives*. WO 0109107.

300940

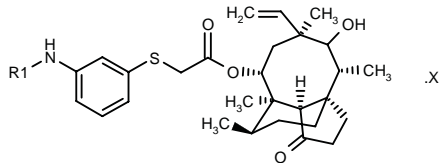
2-[2-*tert*-Butyl-5-(formylamino)phenylsulfanyl]acetic acid (3*aS*,4*R*,6*S*,8*R*,9*R*,9*aR*,10*R*)-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinyl-3*a*,9-propanoperhydrocyclopentacycloocten-8-yl ester

14-*O*-[2-[2-*tert*-Butyl-5-(formylamino)phenylsulfanyl]-acetyl]mutilin



C33 H47 N O5 S; Mol wt: 569.8023

ACTION – Antibacterial agent active against Gram-positive and Gram-negative microorganisms such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Enterococcus faecium*, *Escherichia coli*, *Mycoplasma* and *Chlamydia* including antibiotic-resistant strains. *In vivo*, compound was effective in a murine model of systemic *S. aureus* ATCC 49951 infection, protecting animals from mortality with ED₅₀ values of 7.55 mg/kg s.c. and 7.72 mg/kg p.o. Other exemplified compounds from this series of mutilin derivatives include the following:



Compound	R1	X	Formula
300941	2(R)-Pip-CO	HCl	C ₃₄ H ₄₈ N ₂ O ₅ S.HCl
300942	H		C ₂₈ H ₃₉ NO ₄ S

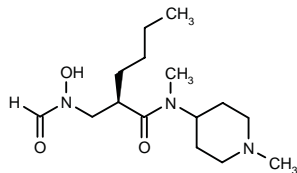
SOURCE – Biochemie.

REFERENCES

1. Ascher, G. et al. (Biochemie GmbH) *Mutilin derivs. and their use as antibacterials*. WO 0109095.

301111

2(*R*)-(N-Formyl-N-hydroxyaminomethyl)-N-methyl-N-(1-methylpiperidin-4-yl)hexanamide



C15 H29 N3 O3; Mol wt: 299.4121

ACTION – A representative compound from a series of *N*-formyl-hydroxylamine derivatives with antibacterial activity, reported to be active against Gram-positive and Gram-negative organisms and to act, at least in part, by inhibiting intracellular bacterial polypeptide deformylase. This compound demonstrated antibacterial activity against *Escherichia coli* DH5α with an MIC of 12.5 μM.

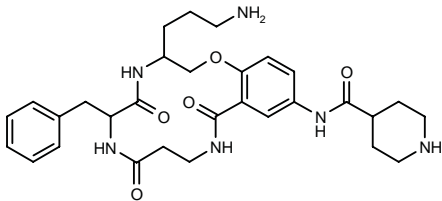
SOURCE – British Biotech.

REFERENCES

1. Hunter, M.G. et al. (British Biotech Pharmaceuticals Ltd.) *Antibacterial agents*. WO 0110835.

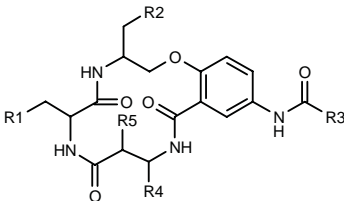
301752

N-[3-(3-Aminopropyl)-6-benzyl-5,8,12-trioxo-3,4,5,6,7,8,9,10,11,12-decahydro-2*H*-1,4,7,11-benzoxatriazacyclopentadecin-14-yl]piperidine-4-carboxamide



C30 H40 N6 O5; Mol wt: 564.6830

ACTION – Antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative microorganisms, as well as enterobacteria and anaerobes, reported to be particularly useful against *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Mycobacterium tuberculosis*. Other specifically claimed macrocyclic compounds are:



Compound	R1	R2	R3	R4	R5	Formula
301753	CONH2	4-OH-Ph	2-pyrazinyl	H	H	C ₂₈ H ₂₉ N ₇ O ₇
301754	CH2CO2H	OH	2-pyrazinyl	H	H	C ₂₃ H ₂₈ N ₆ O ₈
301755	CH2NH-C(=NH)NH2	CH2CH2-NH2	thymin-1-yl- -CH2	CO2H	H	C ₂₈ H ₃₈ N ₁₀ O ₉
301756	OH	H	4-Pip	H	H	C ₂₂ H ₃₁ N ₅ O ₆
301757	CH2CO2H	H	NH2	H	NH2	C ₁₉ H ₂₆ N ₆ O ₇

SOURCE – Isis Pharmaceuticals.

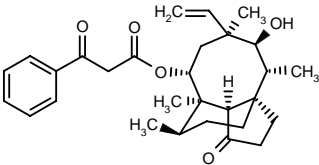
REFERENCES

1. Jefferson, E. and Swayze, E.E. (Isis Pharmaceuticals, Inc.) *Macrocyclic cpds. and preparation methods thereof*. WO 0114346.

301854

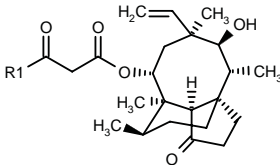
3-Oxo-3-phenylpropionic acid (3*a*S,4*R*,5*S*,6*S*,8*R*,9*R*,9*aR*,10*R*)-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinyl-perhydro-3*a*,9-propanocyclopentacycloocten-8-yl ester

14-*O*-(3-oxo-3-phenylpropionyl)mutilin



C29 H38 O5; Mol wt: 466.6142

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria and mycoplasma such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Haemophilus* sp., *Neisseria* sp., *Legionella* sp., *Chlamydia* sp., *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Mycoplasma gallisepticum*. Other specifically claimed compounds from this series of pleuromutilin β-ketoesters are:



Compound	R1	Formula
301855	3-Pyr	C ₂₈ H ₃₇ NO ₅
301856	4-Pyr	C ₂₈ H ₃₇ NO ₅
301857	1-PhCH2-4-Pip	C ₃₆ H ₄₉ NO ₅
301858	4-quinuclidinyl	C ₂₉ H ₄₃ NO ₅
301859	1-azabicyclo[2.2.1]hept-4-yl	C ₃₀ H ₄₅ NO ₅
301860	CH2Cl	C ₂₄ H ₃₅ ClO ₅
301861	CH2SCH2CH2N(Et)2	C ₃₀ H ₄₉ NO ₅ S
301864	4-quinuclidinyl-SCH2	C ₃₁ H ₄₇ NO ₅ S
301865	2-pyrimidinyl-SCH2	C ₂₈ H ₃₈ N ₂ O ₅ S
301866	CH2SPh	C ₃₀ H ₄₀ O ₅ S
301867	5-NH2-1,3,4-thiadiazol-SCH2	C ₂₆ H ₃₇ N ₅ O ₅ S ₂
301868	6-EtO-2-benzothiazolyl-SCH2	C ₃₃ H ₄₃ NO ₆ S ₂
301869	3-NH2-1,2,4-triazol-5-yl-SCH2	C ₂₆ H ₃₈ N ₄ O ₅ S
301870	4-MeO-Ph	C ₃₀ H ₄₀ O ₆

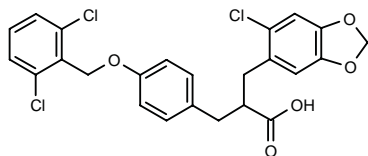
SOURCE – GlaxoSmithKline.

REFERENCES

1. Dean, D.K. et al. (SmithKline Beecham plc) *Pleuromutilin β-ketoesters*. WO 0114310.

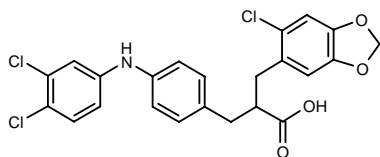
301927

3-(6-Chloro-1,3-benzodioxol-5-yl)-2-[4-(2,6-dichlorobenzoyloxy)benzyl]propionic acid



C₂₄ H₁₉ Cl₃ O₅; Mol wt: 493.7681

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli* and *Klebsiella pneumoniae* including antibiotic-resistant strains; it acts by inhibiting the fatty acid synthase FabH. Another specifically claimed compound is:



301928: C₂₃ H₁₈ Cl₃ N O₄

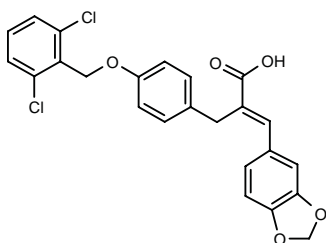
SOURCE – GlaxoSmithKline.

REFERENCES

1. Christensen, S.B. IV et al. (SmithKline Beecham Corp.) *Fatty acid synthase inhibitors*. WO 0114362.

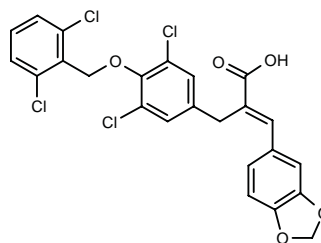
301929

3-(1,3-Benzodioxol-5-yl)-2-[4-(2,6-dichlorobenzoyloxy)-benzyl]-2(E)-propenoic acid



C₂₄ H₁₈ Cl₂ O₅; Mol wt: 457.3072

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli* and *Klebsiella pneumoniae* including antibiotic-resistant strains; it acts by inhibiting the fatty acid synthase FabH. Another specifically claimed compound is:



301931: C₂₄ H₁₆ Cl₄ O₅

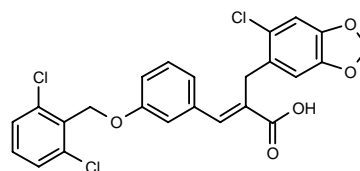
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gaitanopoulos, D. et al. (SmithKline Beecham Corp.) *Fatty acid synthase inhibitors*. WO 0114364.

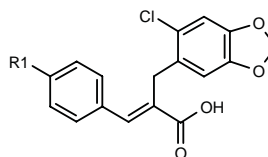
301932

2-(6-Chloro-1,3-benzodioxol-5-ylmethyl)-3-[3-(2,6-dichlorobenzoyloxy)phenyl]-2(E)-propenoic acid



C₂₄ H₁₇ Cl₃ O₅; Mol wt: 491.7523

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli* and *Klebsiella pneumoniae* including antibiotic-resistant strains; it acts by inhibiting the fatty acid synthase FabH. Other specifically claimed compounds are:



Compound	R1	Formula
301934	2,6-(Cl)2-PhCH ₂ O	C ₂₄ H ₁₇ Cl ₃ O ₅
301935	3,5-(Cl)2-PhO	C ₂₃ H ₁₅ Cl ₃ O ₅
301937	2,5-(Cl)2-PhNH	C ₂₃ H ₁₆ Cl ₃ NO ₄
301938	3,5-(Cl)2-Ph	C ₂₃ H ₁₅ Cl ₃ O ₄

SOURCE – GlaxoSmithKline.

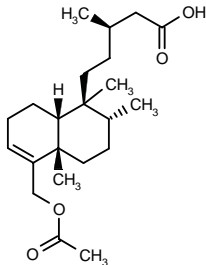
REFERENCES

1. Christensen, S.B. IV et al. (SmithKline Beecham Corp.) *Fatty acid synthase inhibitors*. WO 0114363.

302714

(+)-5-[(1*S*,2*R*,4*aS*,8*aR*)-5-(Acetoxymethyl)-1,2,4*a*-trimethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalen-1-yl]-3(*R*)-methylpentanoic acid

(+)-19-Acetoxy-*cis*-clerodan-3-ene-15-oic acid



C22 H36 O4; Mol wt: 364.5224

ACTION – Antibacterial agent isolated from *Cistus monspeliensis* L. leaves, with significant antibacterial activity against staphylococci (MIC₅₀ = 85 μM) and no cytostatic or cytotoxic activity against human leukemia cell lines.

SOURCES – University of Athens, Athens (GR); NCSR Demokritos, Greece (GR); National Hellenic Research Foundation, Athens (GR); National Institute of Chemistry, Ljubljana, Ljubljana (SI).

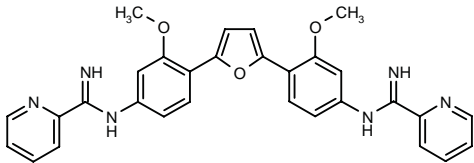
REFERENCES

1. Kolocouris, A. et al. *Structure elucidation and conformational properties of a novel bioactive clerodane diterpene using a combination of high field NMR spectroscopy, computational analysis and X-ray diffraction.* Bioorg Med Chem Lett 2001, 11(6): 837.

ANTIFUNGAL AGENTS

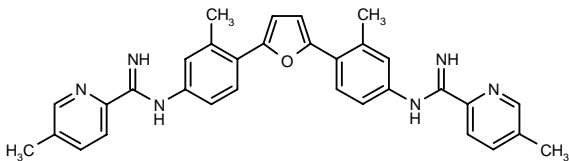
303843

*N*¹,*N*¹'-(2,5-Furandiyl)bis(3-methoxy-4,1-phenylene)bis-(pyridine-2-carboxamide)



C30 H26 N6 O3; Mol wt: 518.5744

ACTION – Antifungal agent with an MIC of approximately 1 μg/ml against a number of *Candida* strains, as well as *Cryptococcus neoformans*, *Aspergillus flavus* and *Rhizopus arrhizus*. Compound showed fungicidal activity against *C. albicans* and *R. arrhizus*. Another related compound is:



303844: C32 H30 N6 O

SOURCES – Duke University, Durham, NC (US); Georgia State University, Atlanta, GA (US); University of Illinois at Chicago, Chicago, IL (US).

REFERENCES

1. Stephens, C.E. et al. *Diguanidino and "reversed" diamidino 2,5-diarylfurans as antimicrobial agents.* J Med Chem 2001, 44(11): 1741.

WF-217

304096

ACTION – A novel antimicrobial substance isolated from the fungus *Chaetomium* sp. No. 217 (FERM BP-6917). WF-217 was active against *Candida albicans* FP633, *Aspergillus fumigatus* FP1305 and *Cryptococcus neoformans* YC203 (MEC = 1.56, 0.04 and 15.6 μg/ml, respectively).

SOURCE – Fujisawa.

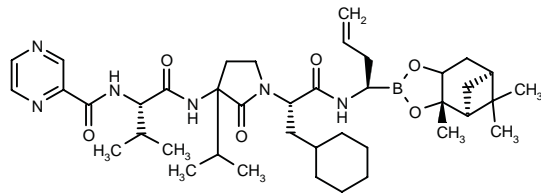
REFERENCES

1. Ohtsu, R. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel cpd., WF217.* WO 0129182.

ANTIVIRAL DRUGS

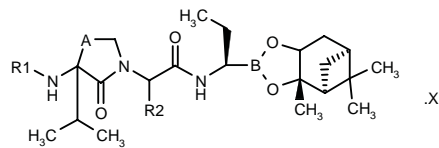
300737

N-[1(*S*)-[1-[1(*S*)-(Cyclohexylmethyl)-2-oxo-2-[1(*R*)-[(1*S*,2*S*,8*S*)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo-[6.1.1.0^{2,6}]dec-4-yl]-3-butenylamino]ethyl]-3-isopropyl-2-oxopyrrolidin-3-ylcarbamoyl]-2-methylpropyl]pyrazine-2-carboxamide



C40 H61 B N6 O6; Mol wt: 732.7689

ACTION – Antiviral agent for the treatment of hepatitis C virus (HCV) infections that acts by inhibiting HCV NS3 protease. Other specifically claimed compounds from this series of lactam derivatives include the following:



Compound	R1	R2	A	X	Formula
300738	H	cyclohexyl-CH2	-CH2-	HCl	C ₂₉ H ₅₀ BN ₃ O ₄ .HCl
300739	CONHPh	cyclohexyl-CH2	-CH2-		C ₃₆ H ₅₅ BN ₄ O ₅
300740	H	Ph	-CH2-	HCl	C ₂₈ H ₄₂ BN ₃ O ₄ .HCl
300741	H	i-Bu	-CH2-	HCl	C ₂₈ H ₄₆ BN ₃ O ₄ .HCl
300742	t-BuOCO	Ph	-(CH2)2-		C ₃₄ H ₅₂ BN ₃ O ₆
300743	3-Me-PhSO2	Ph	-(CH2)2-		C ₃₆ H ₅₀ BN ₃ O ₆ S

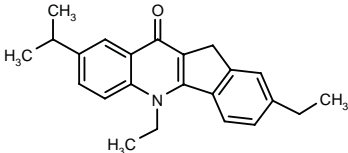
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Priestley, E.S. and Decicco, C.P. (DuPont Pharmaceuticals Co.) *Lactam inhibitors of hepatitis C virus NS3 protease*. WO 0107407.

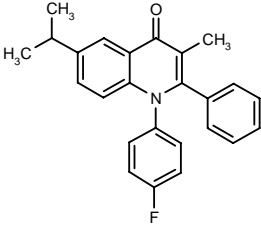
301601

2,5-Diethyl-8-isopropyl-10,11-dihydro-5*H*-indeno[1,2-*b*]-quinolin-10-one



C23 H25 N O; Mol wt: 331.4565

ACTION – Antiviral agent active against picornaviruses, rhinoviruses and rotaviruses, as demonstrated *in vitro* by IC₅₀ values of 0.18, 0.18, 0.71, 0.56, 0.25, 0.20, 0.58 and 0.21 µg/ml, respectively, against poliovirus type 1, echovirus type 11, coxsackievirus type A7 and B4, human rhinovirus type 1B, 2, 14 and 89 in infected HeLaS3 cells and by IC₅₀ values of 0.56 and 0.59 µg/ml, respectively, against human and simian rotavirus in infected MA104 cells. When tested against uninfected HeLaS3 cells, compound gave a CC₅₀ value > 1 µg/ml. Another exemplified compound from this series of 1,2-disubstituted 1,4-dihydro-4-oxoquinolines is:



301603: C25 H22 F N O

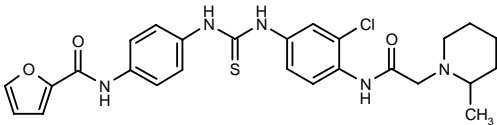
SOURCE – Maruishi Pharmaceutical.

REFERENCES

1. Tamura, T. et al. (Maruishi Pharmaceutical Co., Ltd.) *1,2-Disubstd. 1,4-dihydro-4-oxoquinoline cpds*. EP 1081138, JP 2001064259, JP 2001064261, JP 2001089455, JP 2001089476.

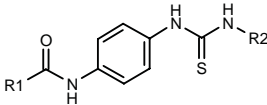
301631

N-[4-[3-[3-Chloro-4-[2-(2-methylpiperidin-1-yl)-acetamido]phenyl]thioureido]phenyl]furan-2-carboxamide



C26 H28 Cl N5 O3 S; Mol wt: 526.0582

ACTION – Antiviral agent active against herpesviruses, including human cytomegalovirus (HCMV), herpes simplex viruses (HSV), Epstein-Barr virus, varicella-zoster virus (VZV), human herpesvirus type 6 and 7 and Kaposi herpesvirus, as demonstrated *in vitro* by IC₅₀ values of 3, 0.7 and 0.09 µg/ml, respectively, against HSV-1 in infected Vero cells and against VZV and HCMV in infected human foreskin fibroblasts. Other exemplified compounds from this series of heterocyclic carboxamide-containing thiourea derivatives include the following:



Compound	R1	R2	Formula
301632	2-furyl	5-Cl-2-N(Me)2-Ph	C ₂₀ H ₁₉ ClN ₄ O ₂ S
301633	1,2,3-thiadiazol-4-yl	3,5-(Br)2-4-NH2-Ph	C ₁₆ H ₁₂ Br ₂ N ₆ OS ₂
301635	2-furyl	3-Cl-PhNH	C ₁₈ H ₁₅ ClN ₄ O ₂ S

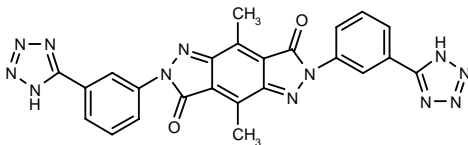
SOURCE – American Home Products.

REFERENCES

1. Bloom, J. et al. (American Home Products Corp.) *Heterocyclic carboxamide-containing thiourea inhibitors of herpes viruses containing phenylenediamine group*. US 6197803.

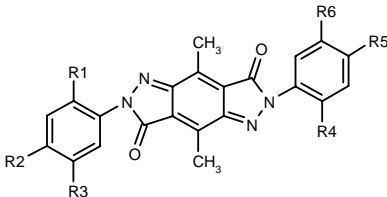
301761

4,8-Dimethyl-2,6-bis[3-(1*H*-tetrazol-5-yl)phenyl]-2,3,6,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]dipyrazole-3,7-dione



C24 H16 N12 O2; Mol wt: 504.4724

ACTION – Antiviral agent for the treatment and prophylaxis of influenza virus infections that acts by inhibiting viral transcriptase. Other specifically claimed compounds from this series of pyrazolo[3,4-*f*]indazole-3,7-dione derivatives include the following:



Compound	R1=R4	R2=R5	R3=R6	Formula
301762	H	1,3,4-thiadiazol-2-yl-NHSO2	H	C ₂₆ H ₁₈ N ₁₀ O ₆ S ₄
301763	H	5-tetrazolyl	H	C ₂₄ H ₁₆ N ₁₂ O ₂
301764	H	H	SO2NH2	C ₂₂ H ₁₈ N ₆ O ₆ S ₂
301766	OMe	H	CO2H	C ₂₆ H ₂₀ N ₄ O ₈
301767	Me	H	CONH2	C ₂₆ H ₂₂ N ₆ O ₄

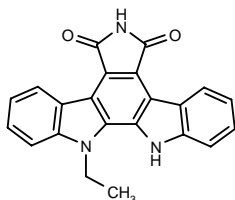
SOURCE – ViroPharma.

REFERENCES

1. Diana, G.D. (ViroPharma, Inc.) *Cpds., compsns. and methods for treating influenza*. WO 0114368.

302181

12-Ethyl-6,7,12,13-tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole-5,7-dione



C22 H15 N3 O2; Mol wt: 353.3795

ACTION – Antiviral agent active against human cytomegalovirus (HCMV), as demonstrated in cell culture by an IC_{50} of 19 nM.

SOURCE – GlaxoSmithKline.

REFERENCES

1. Bonser, R.W. et al. (Glaxo Wellcome plc) *Cpds. for the treatment of restenosis*. WO 9604906.
2. Slater, M.J. et al. (Glaxo Wellcome plc) *Further indole derivs. with antiviral activity*. US 5547976, WO 9318766.
3. Slater, M.J. et al. *Unsymmetrical N-alkyl indolocarbazoles: Potent inhibitors of human cytomegalovirus replication*. Antivir Res 2001, 50(1): Abst 69.

CH-100

302441

Chinese herbal preparation containing Artemisia frigida plant (32 mg), Salvia miltiorrhiza root (32 mg), Taraxacum mongolicum plant (28 mg), Astragalus membranaceus (24 mg), Lanthanum parasiticus stem (24 mg), Paeonia lactiflora root (24 mg), Codonopsis pilosula root (20 mg), Glehnia littoralis plant (20 mg), Polygonum cuspidatum root (20 mg), Bupleurum falcatum root (16 mg), Crataegus pinnatifida fruit (16 mg), Gentiana scabra whole fruit (16 mg), Lycium barbarum fruit (16 mg), Zizyphus jujuba fruit (16 mg), Curcuma longa fruit (16 mg), Glycyrrhiza uralensis root (12 mg), Polyporus umbellatus root (18 mg), Poria cocos root (14 mg) and Panax pseudoginseng root (4 mg)

ACTION – Chinese herbal preparation undergoing clinical evaluation in patients with chronic hepatitis C virus (HCV) infection. Preliminary results indicated that this herbal combination was well tolerated, lowered serum ALT levels and improved symptoms and quality of life in patients with chronic hepatitis C infection.

SOURCES – Cathay Herbal; University of Newcastle at Australia, Newcastle, NS (AU).

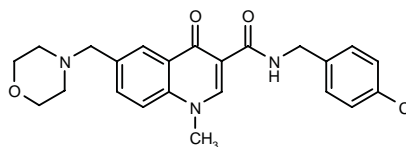
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4. Mollison, L.C. et al. *A randomized double blind, placebo controlled trial of a Chinese herbal preparation (CH100) in chronic hepatitis C*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1968.
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6. Sladden, T.J. et al. *A trial of a Chinese herbal medicine for chronic hepatitis C*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1959.

PNU-183792*

292422

N-(4-Chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide



C23 H24 Cl N3 O3; Mol wt: 425.9136

ACTION – Antiviral agent, a non-nucleoside inhibitor of herpesvirus polymerase with IC_{50} values of 0.66, 0.74 and 0.44 μ M against human cytomegalovirus (HCMV), human herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV) polymerases, respectively, and inactive against human α , γ and δ polymerases ($IC_{50} > 40 \mu$ M). In cell culture, compound inhibited human and rodent cytomegaloviruses in both plaque reduction and virus yield reduction assays ($IC_{50} = 0.3$ -0.5 μ M) and was active against a panel of clinical isolates of HCMV. Compound was also active against VZV ($IC_{50} = 0.3$ -3 μ M) and HSV-1 and HSV-2 ($IC_{50} = 4$ -8 μ M), as well as against a panel of clinical isolates of VZV or HSV-1 and HSV-2. It retained activity against ganciclovir- and cidofovir-resistant CMV strains and aciclovir-resistant HSV strains; no activity was seen against a panel of other DNA and RNA viruses. Compound was orally bioavailable and exerted potent antiviral activity in mice infected with murine CMV.

SOURCE – Pharmacia.

REFERENCES

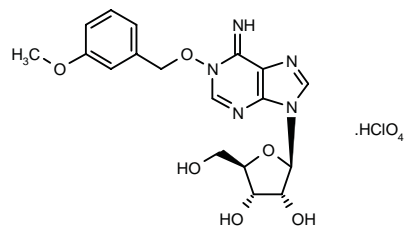
1. Turner, S.R. et al. (Pharmacia Corp.) *4-Oxo-1,4-dihydro-3-quinolinecarboxamides as antiviral agents*. WO 0040563.
2. Brideau, R.J. et al. *Broad spectrum anti-herpesvirus activity of novel 4-oxo-1,4-dihydroquinolines which target the viral polymerase*. Antivir Res 2001, 50(1): Abst 72.

*Identified compound **292422** (see **292420**) Drug Data Rep 2000, 022(11): 1014.

SRI-7055*,1,2

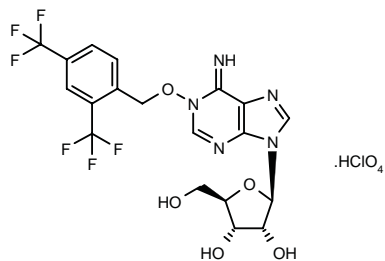
188796

1-(3-Methoxybenzyloxy)adenosine perchlorate



C18 H21 N5 O6 . Cl H O4; Mol wt: 503.8498

ACTION – Antiviral agent active against variola (IC₅₀ = 0.07-0.12 μM) and other orthopoxviruses including monkeypox, cowpox and vaccinia viruses (IC₅₀ = 0.37, 5.70 and 0.44 μM, respectively). Compound did not show cytotoxicity in uninfected Vero cells and it was well tolerated *in vivo* up to 300 mg/kg/day for 4 days. Another adenosine-*N*¹-oxide derivative is:



SRI-6928 [304051]¹⁻³: C19 H17 F6 N5 O5 . Cl H O4

SOURCES – Southern Research Institute, Birmingham, AL (US); U.S. Army Medical Research Institute of Infectious Diseases, Ft. Detrick, MD (US).

REFERENCES

1. Montgomery, J.A. et al. (Southern Research Institute) *Adenosine cpds. useful in the prevention and treatment of vaccinia virus infections*. US 5102873.

2. Baker, R.O. et al. *Activity of adenosine-N1-oxide derivatives against variola and other orthopoxviruses*. Antivir Res 2001, 50(1): Abst 109.

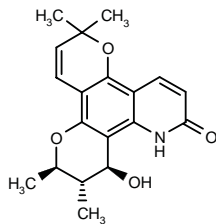
3. Kwong, C.D. et al. *Synthesis and antiviral evaluation of analogs of adenosine-N1-oxide and 1-(benzyloxy) adenosine*. Nucleosides Nucleotides 1998, 17(8): 1409.

*Identified compound **188796** (see **184372**) Drug Data Rep 1992, 014(10): 0923.

AIDS MEDICINES

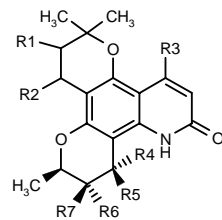
300774

(6*R*,7*S*,8*S*)-8-Hydroxy-2,2,6,7-tetramethyl-7,8,9,10-tetrahydro-2*H*,6*H*-dipyrano[2,3-*f*2',3'-*h*]quinolin-10-one



C19 H21 N O4; Mol wt: 327.3779

ACTION – Antiviral dipyranoquinolinone with a calanolide skeleton, potentially useful as an anti-HIV agent. This compound was found to possess a better therapeutic index than calanolides, overcoming stability and solubility problems. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
300775	bond		H	OH	H	H	Me	C ₁₉ H ₂₁ NO ₄
300776	bond		Me	-O-		Me	H	C ₂₀ H ₂₁ NO ₄
300777	bond		Pr	-O-		Me	H	C ₂₂ H ₂₅ NO ₄
300778	bond		Me	H	OH	Me	H	C ₂₀ H ₂₃ NO ₄
300779	bond		Pr	H	OH	Me	H	C ₂₂ H ₂₇ NO ₄
300780	bond		Pr	OH	H	Me	H	C ₂₂ H ₂₇ NO ₄
300781	bond		Pr	OH	H	H	Me	C ₂₂ H ₂₇ NO ₄
300782	H	H	H	-O-		Me	H	C ₁₉ H ₂₁ NO ₄
300783	H	H	H	H	OH	Me	H	C ₁₉ H ₂₃ NO ₄

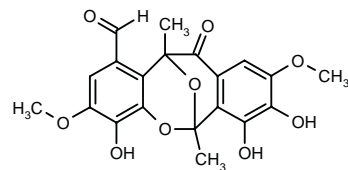
SOURCE – Council of Scientific and Industrial Research, New Delhi (IN).

REFERENCES

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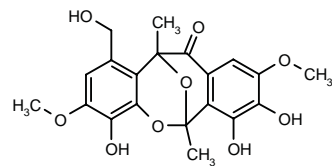
300892

4,7,8-Trihydroxy-3,9-dimethoxy-6,12-dimethyl-11-oxo-11,12-dihydro-6*H*-6,12-epoxydibenzo[*b*,*f*]oxocin-1-carbaldehyde



C20 H18 O9; Mol wt: 402.3532

ACTION – Antiviral agent for AIDS isolated from the aerobic fermentation of a culture of sterile fungus MF6388 (ATCC 74478) or *Ascochyta* sp. MF6591 (ATCC 74477), with HIV integrase-inhibitory activity. Another compound isolated from the same source is:



300893: C20 H20 O9

SOURCE – Merck & Co.

REFERENCES

1. Dombrowski, A. et al. (Merck & Co., Inc.) *HIV integrase inhibitors*. WO 0109114.

VALGANCICLOVIR HYDROCHLORIDE

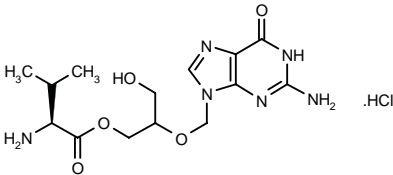
Prop INNM; USAN

233109

5-Amino-3-[1-(hydroxymethyl)-2-(L-valyloxy)ethoxy-methyl]-6,7-dihydro-3*H*-imidazo[4,5-*d*]pyrimidin-7-one hydrochloride

L-Valine 2-(guanin-9-ylmethoxy)-3-hydroxypropyl ester hydrochloride

Ro-10-79070/194
RS-79070⁺-194



C14 H22 N6 O5 . HCl ; Mol wt: 390.8257

ACTION – Ganciclovir prodrug.

INDICATION – Treatment of cytomegalovirus (CMV) retinitis in AIDS patients.

PRESENTATION – Tablets equivalent to 450 mg valganciclovir.

PROPRIETARY NAME – Valcyte (US).

SOURCE – Roche.

REFERENCES

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6. Nestor, J.J. and Maag, H. (Syntex [USA], Inc.) *2-(2-Amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol deriv*. US 5856481.

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11. Chan, R. et al. *An HPLC method for the determination of diastereomeric prodrug RS-79070-004 in human plasma*. J Pharm Biomed Anal 1999, 21(3): 647.

12. Jung, D. and Dorr, A. *Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects*. J Clin Pharmacol 1999, 39(8): 800.

13. Martin, D. et al. *Valganciclovir vs. IV ganciclovir as induction therapy for newly diagnosed cytomegalovirus retinitis: A randomized, controlled study*. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 231.

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15. Pescovitz, M.D. et al. *Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients*. Antimicrob Agents Chemother 2000, 44(10): 2811.

16. Sugawara, M. et al. *Transport of valganciclovir, a ganciclovir prodrug, via peptide transporters PEPT1 and PEPT2*. J Pharm Sci 2000, 89(6): 781.

17. Walmsley, S. and Tseng, A. *Comparative tolerability of therapies for cytomegalovirus retinitis*. Drug Saf 1999, 21(3): 203.

18. *FDA Antiviral Drugs Advisory Committee recommends approval of Roche's valganciclovir*. DailyDrugNews.com (Daily Essentials) 2001, March 1.

19. *Investigational treatment for AIDS-related CMV retinitis filed for approval with FDA*. DailyDrugNews.com (Daily Essentials) 2000, Oct 11.

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21. *Proposed international nonproprietary names (Prop. INN): List 78*. WHO Drug Inf 1997, 11(4): 296.

22. *Valcyte approved by FDA for AIDS-related CMV*. DailyDrugNews.com (Daily Essentials) 2001, April 3.

23. *Valganciclovir, a more potent oral therapy for CMV retinitis in AIDS, approved by FDA*. Clin Infect Dis 2001, 32(9): U2.

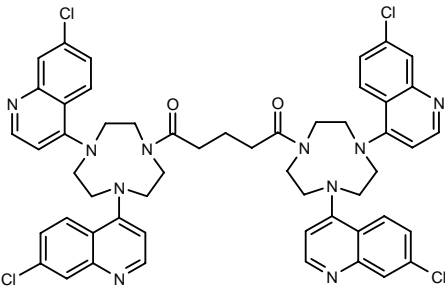
MONOGRAPH – Sorbera, L.A. et al. *Valganciclovir Hydrochloride*. Drugs Fut 2000, 25(5): 0474.

*Drug Data Rep 1997, 019(10): 0929.

TREATMENT OF PROTOZOAL DISEASES

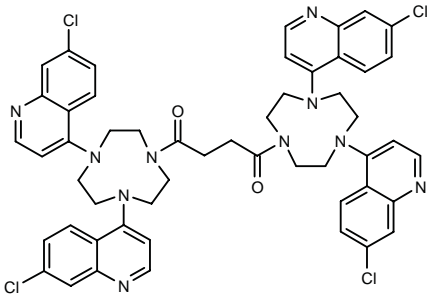
303827

1,5-Bis[4,7-bis(7-chloroquinolin-4-yl)-1,4,7-triazanonan-1-yl]pentan-1,5-dione



C53 H50 Cl4 N10 O2; Mol wt: 1000.8580

ACTION – Antimalarial agent active *in vitro* against chloroquine-resistant *Plasmodium falciparum* (IC₅₀ = 18.3-38.1 nM). Compound was more active than chloroquine (IC₅₀ = 19-175 nM) and was found to inhibit heme polymerization at concentrations similar to chloroquine. Moreover, it did not show cytotoxicity towards human MCR-5 cells and mouse peritoneal macrophages up to 32 μM. Another related tetraquinoline is:



303828: C52 H48 Cl4 N10 O2

SOURCES – CNRS; Tibotec.

REFERENCES

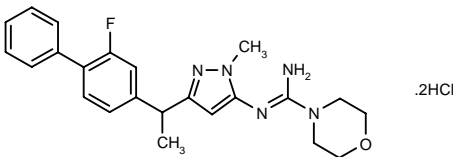
1. Girault, S. et al. *Antiplasmodial activity and cytotoxicity of bis-, tris-, and tetraquinolines with linear or cyclic amino linkers.* J Med Chem 2001, 44(11): 1658.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

300762

N'-[3-[1-(2-Fluorobiphenyl-4-yl)ethyl]-1-methyl-1*H*-pyrazol-5-yl]morpholine-4-carboxamide dihydrochloride



C23 H26 F N5 O . 2HCl; Mol wt: 480.4122

ACTION – A representative compound from a series of heteroaromatic ring compounds with excellent physical properties and potential use in the treatment of immune and inflammatory disorders. In an adjuvant-induced arthritis test in rats, compound produced a significant decrease in edema volume.

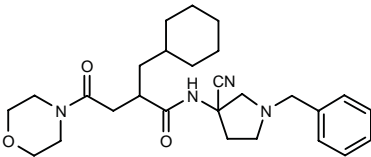
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Nakatsuka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Heteroaromatic ring cpds.* WO 0105774.

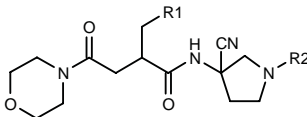
300844

N-(1-Benzyl-3-cyanopyrrolidin-3-yl)-2-(cyclohexylmethyl)-4-(4-morpholinyl)-4-oxobutamide

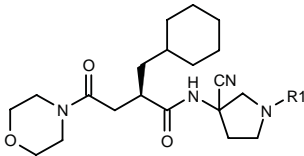


C27 H38 N4 O3; Mol wt: 466.6222

ACTION – Reversible inhibitor of the cysteine proteases cathepsin S, K, F, L and B, potentially useful for the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, multiple sclerosis, psoriasis and glomerulonephritis, as well as Alzheimer’s disease and atherosclerosis. Other specifically claimed compounds from this series of succinate derivatives include the following:



Compound	R1	R2	Formula
300845	cyclohexyl	cyclohexyl	C ₂₆ H ₄₂ N ₄ O ₃
300846	cyclohexyl	cyclopropyl-CH2	C ₂₄ H ₃₈ N ₄ O ₃
300848	cyclohexyl	CH2CH2Ph	C ₂₈ H ₄₀ N ₄ O ₃
300849	cyclohexyl	4-Me-cyclohexyl	C ₂₇ H ₄₄ N ₄ O ₃
300850	4-Me-cyclohexyl	cyclohexyl	C ₂₇ H ₄₄ N ₄ O ₃
300851	1,2,3,4-tetrahydro-2-Naph	cyclohexyl	C ₃₀ H ₄₂ N ₄ O ₃

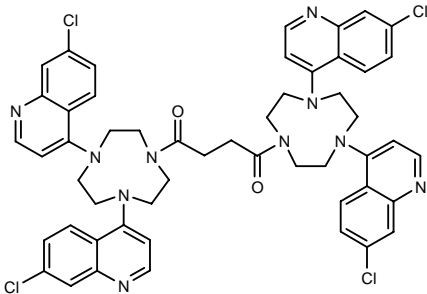


Compound	R1	Isomer	Formula
300852	trans-4-Et-cyclohexyl	3S	C ₂₈ H ₄₆ N ₄ O ₃
300853	trans-3-Me-cyclohexyl	3S	C ₂₇ H ₄₄ N ₄ O ₃
300854	trans-3-Me-cyclohexyl	3R	C ₂₇ H ₄₄ N ₄ O ₃
300855	3,3-(Me)2-cyclohexyl	3S	C ₂₈ H ₄₆ N ₄ O ₃

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Bekkali, Y. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Novel succinate deriv. cpds. useful as cysteine protease inhibitors.* WO 0109110.



303828: C52 H48 Cl4 N10 O2

SOURCES – CNRS; Tibotec.

REFERENCES

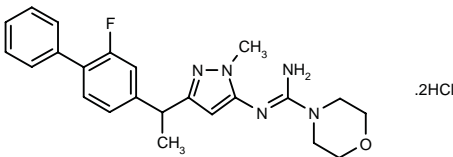
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

300762

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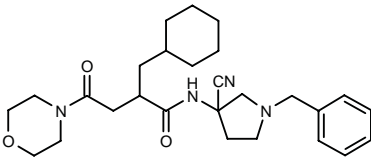
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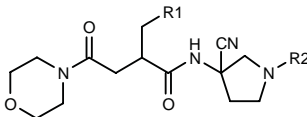
300844

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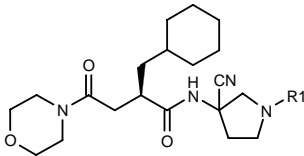


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300849	cyclohexyl	4-Me-cyclohexyl	C ₂₇ H ₄₄ N ₄ O ₃
300850	4-Me-cyclohexyl	cyclohexyl	C ₂₇ H ₄₄ N ₄ O ₃
300851	1,2,3,4-tetrahydro-2-Naph	cyclohexyl	C ₃₀ H ₄₂ N ₄ O ₃



Compound	R1	Isomer	Formula
300852	trans-4-Et-cyclohexyl	3S	C ₂₈ H ₄₆ N ₄ O ₃
300853	trans-3-Me-cyclohexyl	3S	C ₂₇ H ₄₄ N ₄ O ₃
300854	trans-3-Me-cyclohexyl	3R	C ₂₇ H ₄₄ N ₄ O ₃
300855	3,3-(Me)2-cyclohexyl	3S	C ₂₈ H ₄₆ N ₄ O ₃

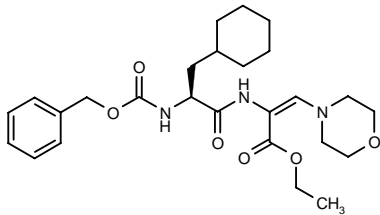
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Bekkali, Y. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Novel succinate deriv. cpds. useful as cysteine protease inhibitors.* WO 0109110.

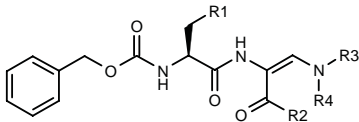
300881

2-[N-(Benzyloxycarbonyl)-3-cyclohexyl-L-alanyl-amino]-3-(4-morpholinyl)-2-propenoic acid ethyl ester



C26 H37 N3 O6; Mol wt: 487.5933

ACTION – Agent for the treatment of muscular dystrophy, osteoporosis, tumor metastasis, rheumatoid arthritis, neuronal or cardiac ischemia, allergic immune response and protozoal or bacterial infections, an inhibitor of cysteine proteases, particularly cathepsins. *In vitro*, compound was shown to inhibit cathepsin B, L, K and S with IC₅₀ values of 0.082, 0.082, 0.37 and 0.0033 μM, respectively. Other exemplified compounds from this series of α-amino acid amide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
300883	i-Pr	NH2	-CH2CH2OCH2CH2-		C ₂₁ H ₃₀ N ₄ O ₅
300884	i-Pr	NHCH2Ph	H	CH2Ph	C ₃₁ H ₃₈ N ₄ O ₄
300885	Ph	OEt	-CH2CH2OCH2CH2-		C ₂₆ H ₃₁ N ₃ O ₆

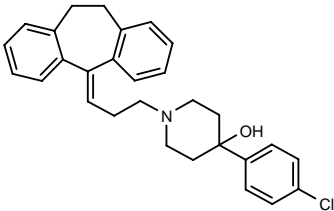
SOURCE – Naeja Pharmaceuticals.

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1. Singh, R. et al. (Naeja Pharmaceuticals Inc.) *Cysteine protease inhibitors*. WO 0109169.

301046

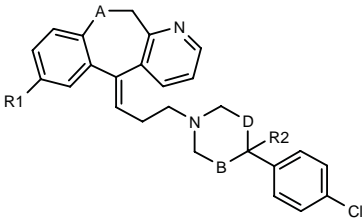
4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)propyl]piperidin-4-ol



C29 H30 Cl N O; Mol wt: 444.0150

ACTION – Chemokine receptor antagonist that inhibits the binding of chemokines such as RANTES, MIP-1α, MCP-2, MCP-3 and MCP-4 to one or more receptors on leukocytes and/or other cell types. It is believed to act as an antagonist at chemokine CCR1 receptors. It was active in inhibiting [¹²⁵I]-RANTES or [¹²⁵I]-MIP-1α binding to receptors in membranes from THP-1 cells (IC₅₀ < 1 μM). This compound may be useful for the treatment of

inflammatory diseases such as arthritis, atherosclerosis, restenosis, ischemia–reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel disease, transplant rejection and asthma. Other exemplified compounds include the following:



Compound	R1	R2	A	B=D	Formula
301047	OCH2CH2OH	OH	O	-CH2-	C ₂₉ H ₃₁ ClN ₂ O ₄
301048	H	OH	S	-CH2-	C ₂₇ H ₂₇ ClN ₂ OS
301049	OH	H	O	-CH2-	C ₂₇ H ₂₇ ClN ₂ O ₂
301050	OCH2C(Me)2OH	OH	O	-CH2-	C ₃₁ H ₃₅ ClN ₂ O ₄
301051	OMe	H	O	-CH2O-	C ₂₈ H ₂₉ ClN ₂ O ₄
301053	CH2CH2OH	OH	O	-CH2-	C ₂₉ H ₃₁ ClN ₂ O ₃
301054	cyclohexyl-OCOCH(Me)OCO	OH	O	-CH2-	C ₃₇ H ₄₁ ClN ₂ O ₇
301055	t-BuCOOCH2OCO	OH	O	-CH2-	C ₃₄ H ₃₇ ClN ₂ O ₆

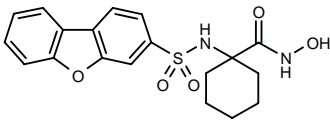
SOURCES – Kyowa Hakko; Millennium.

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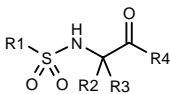
301325

1-(Dibenzofuran-3-ylsulfonamido)cyclohexanecarboxylic acid



C19 H20 N2 O5 S; Mol wt: 388.4420

ACTION – An inhibitor of matrix metalloproteinases (MMPs) that gave IC₅₀ values of 0.295, 0.0017, 0.0045, 0.0155, 4.05, 0.135, 0.049 and 0.0039 μM, respectively, against collagenase 1 (MMP-1), gelatinase A (MMP-2; catalytic-domain and full-length enzyme), stromelysin 1 (MMP-3), matrilysin (MMP-7), gelatinase B (MMP-9), collagenase 3 (MMP-13) and membrane-type MMP-1 (MMP-14). Potentially useful in the treatment of a broad range of disorders including arthritis, multiple sclerosis, atherosclerosis, restenosis, inflammation, pain, aortic aneurysm, heart failure, osteoporosis, periodontal disease, corneal ulceration, burns, decubital ulcers, wounds, cancer, autoimmune and inflammatory disorders dependent upon tissue invasion by leukocytes, acute and chronic neurodegenerative disorders, renal disease and left ventricular dilatation. Other exemplified compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
301326	3-dibenzofuryl	-(CH2)5-		OH	C ₁₉ H ₁₉ NO ₅ S
301327	3-dibenzofuryl	Me	Me	OH	C ₁₆ H ₁₅ NO ₅ S
301328	3-dibenzofuryl	Me	Me	NHOH	C ₁₆ H ₁₆ N ₂ O ₅ S
301329	3-dibenzofuryl	-CH2CH2OCH2CH2-		NHOH	C ₁₈ H ₁₈ N ₂ O ₆ S
301330	7-Br-2-dibenzofuryl	-(CH2)4-		NHOH	C ₁₈ H ₁₇ BrN ₂ O ₅ S
301331	7-Cl-2-dibenzofuryl	Me	Me	NHOH	C ₁₆ H ₁₅ ClN ₂ O ₅ S

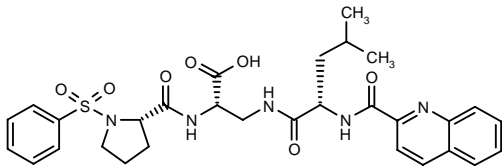
SOURCE – Pfizer.

REFERENCES

1. Conrad, C.A. et al. (Pfizer Inc.) *Hydroxamic acid cpds. useful as matrix metalloproteinase inhibitors*. WO 0112592.

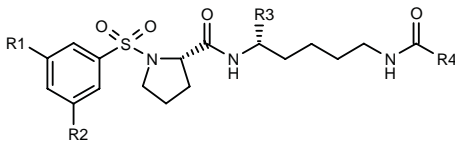
301436

N-[1-(Phenylsulfonyl)-L-prolyl]-3-[N-(quinolin-2-ylcarbonyl)-L-leucylamino]-L-alanine

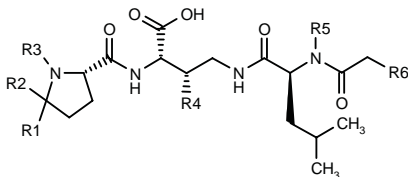


C30 H35 N5 O7 S; Mol wt: 609.7005

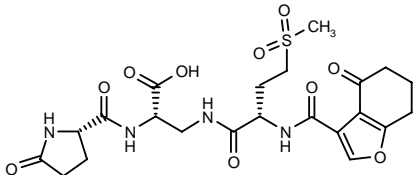
ACTION – Cell adhesion inhibitor that binds specifically to VLA-4 and is particularly useful for the treatment of inflammatory and immune diseases. Other exemplified nonpeptide compounds include the following:



Compound	R1=R2	R3	R4	Formula
301444	H	CH2CO2H	4-oxo-4,5,6,7-tetrahydro-3-benzofuryl	C ₂₇ H ₃₃ N ₃ O ₈ S
301445	Cl	CH2CO2H	1-[3,5-(Cl)2-PhSO2]-2(S)-pyrrolidinyl	C ₂₉ H ₃₄ Cl ₄ N ₄ O ₈ S ₂
301446	H	CO2H	4-OH-PhCH2	C ₂₅ H ₃₁ N ₃ O ₇ S
301447	H	CO2H	4-(Ph-ethynylene)-PhCH2	C ₃₃ H ₃₅ N ₃ O ₆ S



Compound	R1	R2	R3	R4	R5	R6	Formula
301448	-O-		H	H	Me	4-(2-Me-PhNH-CONH)-Ph	C ₃₂ H ₄₂ N ₆ O ₇
301449	H	H	3,5-(Cl)2-PhSO2	H	Me	4-(2-Me-PhNH-CONH)-Ph	C ₃₈ H ₄₆ Cl ₂ N ₆ O ₈ S
301450	H	H	SO2Ph	Ph	H	H	C ₂₉ H ₃₈ N ₄ O ₇ S



301443: C22 H28 N4 O10 S

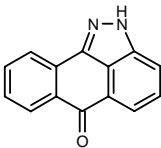
SOURCE – Biogen.

REFERENCES

1. Lee, W.-C. et al. (Biogen, Inc.) *Cell adhesion inhibitors*. WO 0112186.

301539

Anthra[1,9-*cd*]pyrazol-6(2*H*)-one



C14 H8 N2 O; Mol wt: 220.2302

ACTION – A preferred compound from a series of pyrazoloanthrone derivatives that selectively inhibits c-Jun *N*-terminal kinase (JNK). When tested for its inhibitory activity, the compound gave IC₅₀ values of 0.11 μM for JNK1 and JNK2, and 0.15 μM for JNK3 versus > 20 μM for other protein kinases. This compound inhibited lipopolysaccharide (LPS)-induced TNF-α production in mice and was effective in an adjuvant-induced arthritis model in rats, inhibiting paw swelling, joint destruction, transcription factor AP-1 activation and MMP-13 expression. It was also able to reduce the kainic acid-induced seizure response in rats. It is potentially useful for the treatment of arthritis, cancer, gout, asthma, bronchitis, cystic fibrosis, inflammatory gastrointestinal disorders, psoriasis, atherosclerosis, restenosis, stroke, transplant rejection and neurological degenerative disorders.

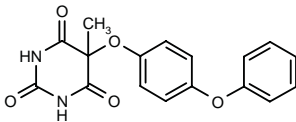
SOURCE – Signal (Celgene).

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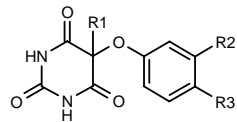
301550

5-Methyl-5-(4-phenoxyphenoxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione



C17 H14 N2 O5; Mol wt: 326.3066

ACTION – Matrix metalloproteinase (MMP) inhibitor that selectively inhibits MMP-13 (collagenase 3) with respect to MMP-1 (fibroblast collagenase). Potentially useful in the treatment of a wide variety of disorders including arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, Alzheimer’s disease, restenosis, osteoporosis, atherosclerosis and stroke. Other specifically claimed pyrimidine-2,4,6-trione derivatives are:



Compound	R1	R2	R3	Formula
301551	Me	H	4-F-PhO	C ₁₇ H ₁₃ FN ₂ O ₅
301552	Bu	H	OPh	C ₂₀ H ₂₀ N ₂ O ₅
301553	Bu	H	4-F-PhO	C ₂₀ H ₁₉ FN ₂ O ₅
301554	Me	H	Ph	C ₁₇ H ₁₄ N ₂ O ₄
301555	Me	Ph	H	C ₁₇ H ₁₄ N ₂ O ₄
301556	Me	H	OCH2Ph	C ₁₈ H ₁₆ N ₂ O ₅

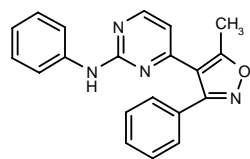
SOURCE – Pfizer.

REFERENCES

1. Blagg, J. (Pfizer Products Inc.) *Pyrimidine-2,4,6-trione metalloproteinase inhibitors*. WO 0112611.

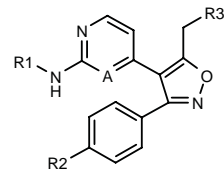
301576

4-(5-Methyl-3-phenylisoxazol-4-yl)-N-phenylpyrimidin-2-amine



C20 H16 N4 O; Mol wt: 328.3734

ACTION – An inhibitor of c-Jun N-terminal kinase (JNK) such as JNK3 (K_i < 0.1 μM), also reported to inhibit Src family kinases, especially Src and Lck. Potentially useful for the treatment or prevention of a broad range of disorders including inflammatory and autoimmune diseases, destructive bone disorders, proliferative and neurodegenerative diseases, infectious diseases, ischemia–reperfusion injury and angiogenesis-related conditions. Other exemplified compounds from this series of five-membered heterocyclic derivatives include the following:



Compound	R1	R2	R3	A	Formula
301578	3-MeS-Ph	H	H	N	C ₂₁ H ₁₈ N ₄ OS
301580	3-Ac-Ph	H	H	N	C ₂₂ H ₁₈ N ₄ O ₂
301582	3-CN-Ph	H	H	CH	C ₂₂ H ₁₆ N ₄ O
301584	6-MeO-2-Naph	H	H	N	C ₂₅ H ₂₀ N ₄ O ₂
301585	3-NO2-PhCO	H	H	N	C ₂₁ H ₁₅ N ₅ O ₄
301586	2-thienyl-CO	H	H	N	C ₁₉ H ₁₄ N ₄ O ₂ S
301587	cyclohexyl	F	OCH2Ph	N	C ₂₇ H ₂₇ FN ₄ O ₂
301588	cyclohexyl	F	1,1-dioxo-tetrahydro-3-thienyl-O	N	C ₂₄ H ₂₇ FN ₄ O ₄ S

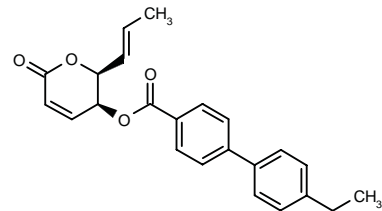
SOURCE – Vertex.

REFERENCES

1. Green, J. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases*. WO 0112621.

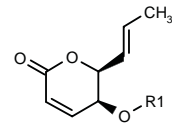
301642

4'-Ethylbiphenyl-4-carboxylic acid 6-oxo-2(S)-[1(E)-propenyl]-3,6-dihydro-2H-pyran-3(S)-yl ester



C23 H22 O4; Mol wt: 362.4228

ACTION – An inhibitor of the production of cytokines, particularly IL-1β (IC₅₀ = 0.1 μM in lipopolysaccharide-stimulated human peripheral blood mononuclear cells [PBMCs]), claimed for the treatment of immunoinflammatory disorders such as rheumatoid arthritis, osteoarthritis, septic shock, psoriasis, atherosclerosis, inflammatory bowel disease, Crohn’s disease and asthma. Within this series of 5,6-dihydro-α-pyrone derivatives, the following are also included:



Compound	R1	Formula
301643	4-Ph-PhCH2	C ₂₁ H ₂₀ O ₃
301645	4-Ph-PhCO	C ₂₁ H ₁₈ O ₄
301648	1-fluorenyl-CO	C ₂₂ H ₁₈ O ₄
301649	9-oxo-1-fluorenyl-CO	C ₂₂ H ₁₆ O ₅
301650	2-Naph-CH=CHCO	C ₂₁ H ₁₈ O ₄
301651	4-C5H11-PhCO	C ₂₀ H ₂₄ O ₄

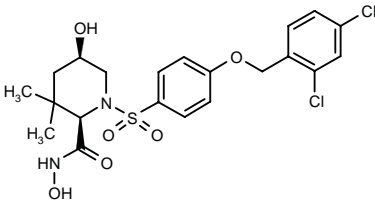
SOURCES – Cubist; Suntory.

REFERENCES

1. Hayes, M.A. et al. (Suntory Ltd.;Cubist Pharmaceuticals, Inc.) *Cytokine production inhibitors*. US 6197811.

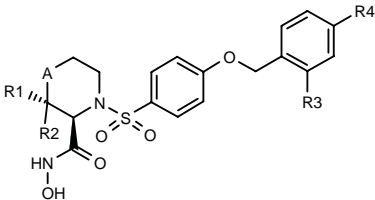
301652

1-[4-(2,4-Dichlorobenzyloxy)phenylsulfonyl]-5(R)-hydroxy-3,3-dimethylpiperidine-2(R)-carbohydroxamic acid



C21 H24 Cl2 N2 O6 S; Mol wt: 503.4006

ACTION – An inhibitor of aggrecanase and other enzymes implicated in joint disease, particularly matrix metalloproteinases (MMPs), potentially useful for the treatment of conditions characterized by the destruction of articular cartilage such as osteoarthritis. *In vitro*, compound was shown to inhibit aggrecanase and MMP-13 with IC₅₀ values < 10 nM, while it exhibited IC₅₀ values in the range 200-1000 nM and in the range 20-40 μM for for MMP-1 and TACE, respectively. Other exemplified compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
301653	OH	Me	Cl	Cl	-CH2-	C ₂₀ H ₂₂ Cl ₂ N ₂ O ₆ S
301655	Me	H	Me	H	-N(COCH2NH2)-	C ₂₂ H ₂₈ N ₄ O ₆ S

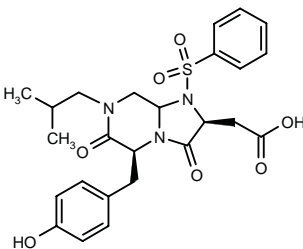
SOURCE – Pfizer.

REFERENCES

1. Noe, M.C. et al. (Pfizer Products Inc.) *Selective inhibitors of aggrecanase in osteoarthritis treatment*. EP 1081137, JP 2001114765.

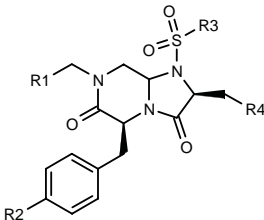
301954

2-[(2S,5S)-5-(4-Hydroxybenzyl)-7-isobutyl-3,6-dioxo-1-(phenylsulfonyl)octahydroimidazo[1,2-a]pyrazin-2-yl]acetic acid



C25 H29 N3 O7 S; Mol wt: 515.5841

ACTION – A representative compound from a series of conformationally constrained derivatives that mimic the secondary structure of reverse-turn regions of biologically active peptides, particularly α₄β₁ and α₄β₇ integrins. *In vitro*, compound was found to displace CS1 peptide from Ramos cells with an IC₅₀ value below 10 μM. Potentially useful for the treatment of inflammatory or cell adhesion-mediated disorders such as rheumatoid arthritis, Alzheimer's disease, adult respiratory distress syndrome (ARDS), asthma, allergies, inflammatory bowel disease, CNS inflammation, atopic dermatitis, encephalitis, multiple sclerosis, meningitis, nephritis, psoriasis, type 1 diabetes, cancer, atherosclerosis, stroke, myocardial ischemia and restenosis. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
301955	CH2CO2H	H	4-Cl-Ph	CH2CO2H	C ₂₅ H ₂₆ ClN ₃ O ₈ S
301956	i-Pr	OH	4-Cl-Ph	CO2H	C ₂₅ H ₂₆ ClN ₃ O ₇ S
301957	CH2CO2H	F	4-Cl-Ph	CH2CO2H	C ₂₅ H ₂₅ ClFN ₃ O ₈ S
301958	CH2CO2H	H	2-Naph	CH2CO2H	C ₂₉ H ₂₉ N ₃ O ₈ S
301959	CH2CO2H	F	2-Naph	CH2CO2H	C ₂₉ H ₂₈ FN ₃ O ₈ S
301960	2-Pyr	H	2-Naph	CH2CO2H	C ₃₂ H ₃₀ N ₄ O ₆ S
301961	Pr	H	2-Naph	CH2CO2H	C ₃₀ H ₃₃ N ₃ O ₆ S
301962	CH2Ph	H	2-Naph	CH2CO2H	C ₃₄ H ₃₃ N ₃ O ₆ S
301963	i-Pr	F	2-Naph	CH2CO2H	C ₃₀ H ₃₂ FN ₃ O ₆ S

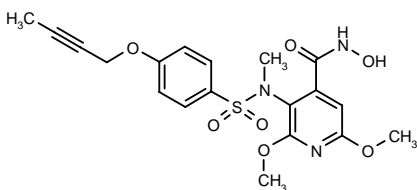
SOURCE – Molecumetics.

REFERENCES

1. Stasiak, M. and Kahn, M. (Molecumetics Ltd.) *Reverse-turn mimetics and methods relating thereto*. WO 0116135.

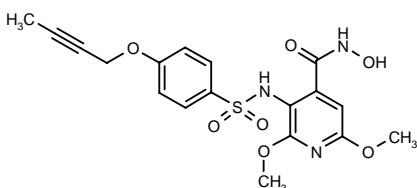
302001

3-[N-[4-(2-Butynyloxy)phenylsulfonyl]-N-methylamino]-2,6-dimethoxypyridine-4-carbohydroxamic acid



C19 H21 N3 O7 S; Mol wt: 435.4549

ACTION – An inhibitor of TNF- α -converting enzyme (TACE; IC₅₀ = 11 nM) and matrix metalloproteinases (MMPs; IC₅₀ = 10,000, 607 and 478 nM, respectively, against MMP-1, MMP-9 and MMP-13) proven to inhibit lipopolysaccharide-stimulated TNF- α production in human mono-cytic THP-1 cells (31% inhibition at 3 μ M). Potentially useful in the treatment of rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory diseases of the CNS, inflammatory bowel disease and HIV infection. Another specifically claimed compound from this series of acetylenic aryl or heteroaryl sulfonamide and phosphinic acid amide hydroxamic acid derivatives is:



302002: C18 H19 N3 O7 S

SOURCE – American Home Products.

REFERENCES

1. Levin, J.I. et al. (American Cyanamid Co.) *Heteroaryl acetylenic sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors*. US 6200996.

[Met(O)⁶,Phe(4F)¹²]DEACETYL-THYMOSIN β_4

304304

L-Seryl-L-aspartyl-L-lysyl-L-prolyl-L-aspartyl-(4-S-oxide)-L-methionyl-L-alanyl-L-glutamyl-L-isoleucyl-L-glutamyl-L-lysyl-(4'-fluoro)-L-phenylalanyl-L-aspartyl-L-lysyl-L-seryl-L-lysyl-L-leucyl-L-lysyl-L-lysyl-L-threonyl-L-glutamyl-L-threonyl-L-glutaminyl-L-glutamyl-L-lysyl-L-asparaginy-L-prolyl-L-leucyl-L-prolyl-L-seryl-L-lysyl-L-glutamyl-L-threonyl-L-isoleucyl-L-glutamyl-L-glutaminyl-L-glutamyl-L-lysyl-L-glutaminyl-L-alanyl-glycyl-L-glutamyl-L-serine

C210 H347 F N56 O78 S; Mol wt: 4955.4290

ACTION – Antiinflammatory agent, a deacetyl-thymosin β_4 analogue with strong antiinflammatory activity against carrageenan-induced edema in mouse paw at 10 and 20 μ g/kg.

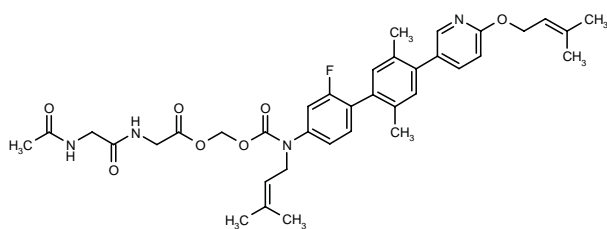
SOURCE – Shinwa Pharmaceutical.

REFERENCES

1. Abiko, T. and Ogawa, R. *Syntheses of two deacetyl-thymosin beta4 analogs and their anti-inflammatory effect on carrageenin-induced edema in the mouse paw*. Mediators Inflamm 2001, 10(2): 89.

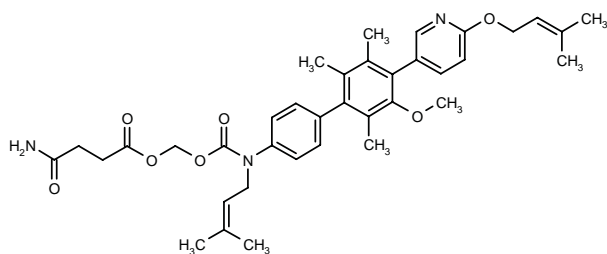
IMMUNOMODULATING AGENTS**300650**

N-Acetyl-glycyl-glycine N-[2-fluoro-2',5'-dimethyl-4'-[6-(3-methyl-2-butenyloxy)pyridin-3-yl]biphenyl-4-yl]-N-(3-methyl-2-butenyl)carbamoyloxymethyl ester



C37 H43 F N4 O7; Mol wt: 674.7657

ACTION – A representative compound from a series of acyloxymethoxycarbonyl prodrugs of previously reported tricyclic immunosuppressive and antiallergic agents, proven to provide substantially increased levels of the parent drug in rats following oral administration compared to direct oral administration of the active drug. In addition, compound was found to completely inhibit ovalbumin-induced IgE antibody production in sensitized rats at 10 mg/kg p.o., being more effective than the parent compound. Another exemplified compound is:



300657: C37 H45 N3 O7

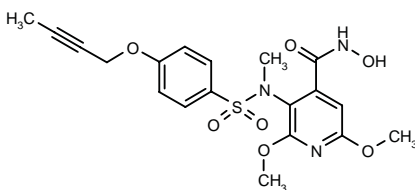
SOURCE – Shionogi.

REFERENCES

1. Aono, K. et al. (Shionogi & Co. Ltd.) *Tricyclic cpds. bearing acyloxymethoxycarbonyl pendants*. WO 0105768.

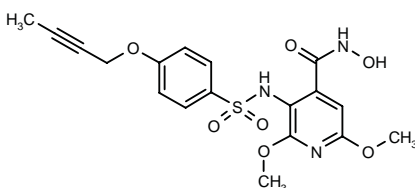
302001

3-[N-[4-(2-Butynyloxy)phenylsulfonyl]-N-methylamino]-2,6-dimethoxypyridine-4-carbohydroxamic acid



C19 H21 N3 O7 S; Mol wt: 435.4549

ACTION – An inhibitor of TNF- α -converting enzyme (TACE; IC₅₀ = 11 nM) and matrix metalloproteinases (MMPs; IC₅₀ = 10,000, 607 and 478 nM, respectively, against MMP-1, MMP-9 and MMP-13) proven to inhibit lipopolysaccharide-stimulated TNF- α production in human mono-cytic THP-1 cells (31% inhibition at 3 μ M). Potentially useful in the treatment of rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory diseases of the CNS, inflammatory bowel disease and HIV infection. Another specifically claimed compound from this series of acetylenic aryl or heteroaryl sulfonamide and phosphinic acid amide hydroxamic acid derivatives is:



302002: C18 H19 N3 O7 S

SOURCE – American Home Products.

REFERENCES

1. Levin, J.I. et al. (American Cyanamid Co.) *Heteroaryl acetylenic sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors*. US 6200996.

[Met(O)⁶,Phe(4F)¹²]DEACETYL-THYMOSIN β_4

304304

L-Seryl-L-aspartyl-L-lysyl-L-prolyl-L-aspartyl-(4-S-oxide)-L-methionyl-L-alanyl-L-glutamyl-L-isoleucyl-L-glutamyl-L-lysyl-(4'-fluoro)-L-phenylalanyl-L-aspartyl-L-lysyl-L-seryl-L-lysyl-L-leucyl-L-lysyl-L-lysyl-L-threonyl-L-glutamyl-L-threonyl-L-glutaminyl-L-glutamyl-L-lysyl-L-asparaginy-L-prolyl-L-leucyl-L-prolyl-L-seryl-L-lysyl-L-glutamyl-L-threonyl-L-isoleucyl-L-glutamyl-L-glutaminyl-L-glutamyl-L-lysyl-L-glutaminyl-L-alanyl-glycyl-L-glutamyl-L-serine

C210 H347 F N56 O78 S; Mol wt: 4955.4290

ACTION – Antiinflammatory agent, a deacetyl-thymosin β_4 analogue with strong antiinflammatory activity against carrageenan-induced edema in mouse paw at 10 and 20 μ g/kg.

SOURCE – Shinwa Pharmaceutical.

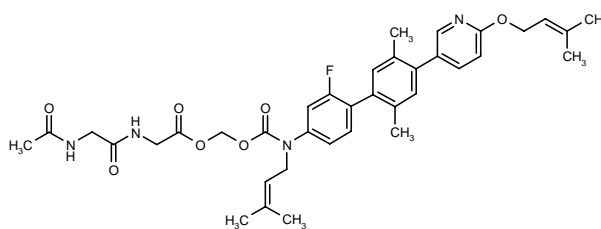
REFERENCES

1. Abiko, T. and Ogawa, R. *Syntheses of two deacetyl-thymosin beta4 analogs and their anti-inflammatory effect on carrageenin-induced edema in the mouse paw*. Mediators Inflamm 2001, 10(2): 89.

IMMUNOMODULATING AGENTS

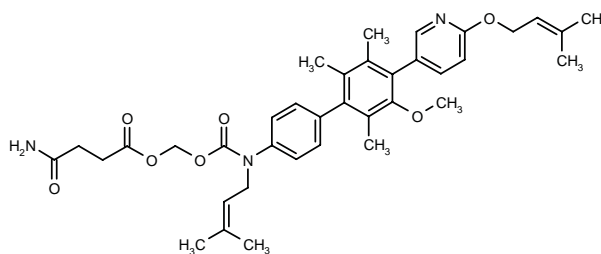
300650

N-Acetyl-glycyl-glycine N-[2-fluoro-2',5'-dimethyl-4'-[6-(3-methyl-2-butenyloxy)pyridin-3-yl]biphenyl-4-yl]-N-(3-methyl-2-butenyl)carbamoyloxymethyl ester



C37 H43 F N4 O7; Mol wt: 674.7657

ACTION – A representative compound from a series of acyloxymethoxycarbonyl prodrugs of previously reported tricyclic immunosuppressive and antiallergic agents, proven to provide substantially increased levels of the parent drug in rats following oral administration compared to direct oral administration of the active drug. In addition, compound was found to completely inhibit ovalbumin-induced IgE antibody production in sensitized rats at 10 mg/kg p.o., being more effective than the parent compound. Another exemplified compound is:



300657: C37 H45 N3 O7

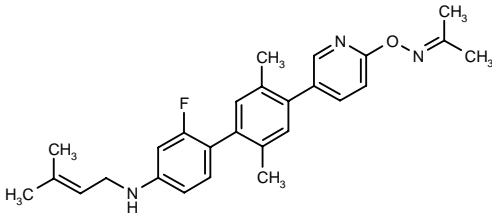
SOURCE – Shionogi.

REFERENCES

1. Aono, K. et al. (Shionogi & Co. Ltd.) *Tricyclic cpds. bearing acyloxymethoxycarbonyl pendants*. WO 0105768.

300660

Propan-2-one O-[5-[2'-fluoro-2,5-dimethyl-4'-(3-methyl-2-butenylamino)biphenyl-4-yl]pyridin-2-yl]oxime



C27 H30 F N3 O; Mol wt: 431.5520

ACTION – Immunosuppressive and antiallergic agent proven to completely inhibit ovalbumin-induced IgE antibody production in sensitized rats at 40 mg/kg p.o.

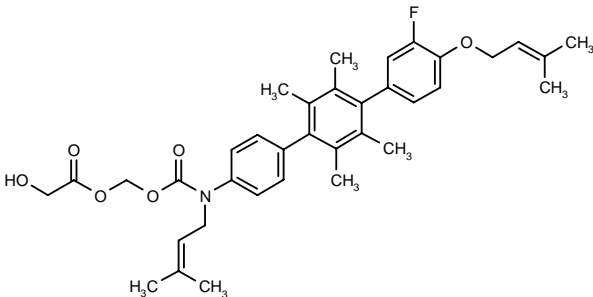
SOURCE – Shionogi.

REFERENCES

1. Tanimoto, N. and Inagaki, M. (Shionogi & Co. Ltd.) *Tricyclic cpds. and drug compsns. containing the same.* WO 0107401.

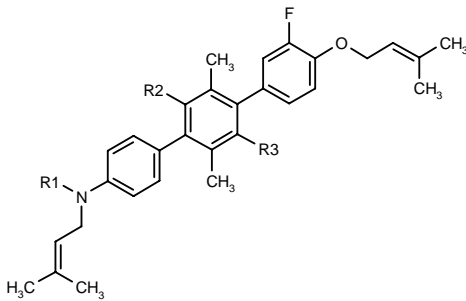
300661

2-Hydroxyacetic acid N-[3''-fluoro-2',3',5',6'-tetramethyl-4''-(3-methyl-2-butenyloxy)-1,1':4',1''-terphenyl-4-yl]-N-(3-methyl-2-butenyl)carbamoyloxymethyl ester



C36 H42 F N O6; Mol wt: 603.7268

ACTION – Prodrug of a previously reported *p*-terphenyl derivative with immunosuppressive and antiallergic activity, proven to provide substantially increased levels of the parent drug following oral administration compared to direct oral administration of the active agent in rats. Within this series of acyloxymethoxycarbonyl prodrugs of *p*-terphenyl compounds, the following are also included:



Compound	R1	R2	R3	Formula
300662	H	Me	Me	C ₃₂ H ₃₈ FNO
300663	CO2CH2OCOCH2OH	Me	OMe	C ₃₆ H ₄₂ FNO ₇
300664	H	Me	OMe	C ₃₂ H ₃₈ FNO ₂
300665	CO2CH2OCOCH2OH	CO2Me	Me	C ₃₇ H ₄₂ FNO ₈
300671	H	CO2Me	Me	C ₃₃ H ₃₈ FNO ₃

SOURCE – Shionogi.

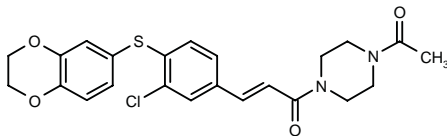
REFERENCES

1. Aono, K. et al. (Shionogi & Co. Ltd.) *p-Terphenyl cpds. bearing acyloxy-methoxycarbonyl side chains.* WO 0105750.

A-292949

302788

1-Acetyl-4-[3-[3-chloro-4-(2,3-dihydro-1,4-benzodioxin-6-yl)sulfanyl]phenyl]-2(*E*)-propenoyl]piperazine



C23 H23 Cl N2 O4 S; Mol wt: 458.9637

ACTION – Potent inhibitor of the interaction between leukocyte function-associated antigen-1 (LFA-1) and intracellular adhesion molecule-1 (ICAM-1), potentially useful for the treatment of inflammatory diseases and graft rejection. Compound inhibited LFA-1/ICAM-1 binding with an IC₅₀ of 40 nM and showed functional antagonist activity by blocking the adherence of LFA-1-expressing JY-8 cells to immobilized ICAM-1 with an IC₅₀ of 80 nM. Compound showed a discrete aqueous solubility and pharmacokinetic profile in rats, with an oral bioavailability of approximately 12%.

SOURCE – Abbott.

REFERENCES

1. Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds.* US 6110922, WO 0039081.

2. Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds.* WO 0059880.

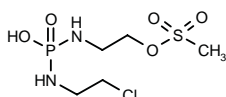
3. Liu, G. et al. *Novel p-arylthio cinnamides as antagonists of leukocyte function-associated antigen-1/intracellular adhesion molecule-1 interaction. 2. Mechanism of inhibition and structure-based improvement of pharmaceutical properties.* J Med Chem 2001, 44(8): 1202.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

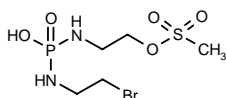
301619

N-(2-Chloroethyl)-*N*'-[2-(methylsulfonyloxy)ethyl]-phosphorodiamidic acid



C₅ H₁₄ Cl N₂ O₅ P S; Mol wt: 280.6676

ACTION – Antineoplastic agent reported to be particularly useful for the treatment of mammary, colon and brain tumors. *In vivo*, compound exhibited antitumor activity against murine leukemia P388, murine sarcoma M5076 and murine mammary 16/C tumors, being superior to cyclophosphamide and ifosfamide, and it was found to be comparable in potency to ifosfamide and superior to cyclophosphamide in a human mammary tumor MCF-7 xenograft model. Another exemplified isophosphoramidate mustard analogue is:



301621: C₅ H₁₄ Br N₂ O₅ P S

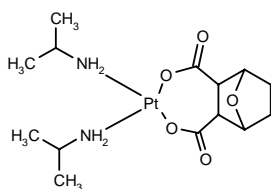
SOURCE – Southern Research Institute, Birmingham, AL (US).

REFERENCES

1. Struck, R.F. (Southern Research Institute) *Isophosphoramidate mustard analogs and use thereof*. US 6197760.

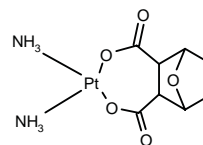
303765

(*SP*-4-2)-Bis(isopropylamine- κ N)[7-oxabicyclo[2.2.1]-heptane-2,3-dicarboxylato(2-)- κ O², κ O³]platinum



C₁₄ H₂₆ N₂ O₅ Pt; Mol wt: 497.4484

ACTION – Antineoplastic agent, a new TCM–platinum complex derived from the combination of demethylcantharidin, a modified component of a Chinese traditional medicine, with a platinum moiety. Compound showed cytotoxic activity against a panel of cancer cell lines including murine leukemia L1210 cells (IC₅₀ = 12.08 μM), human colon carcinoma COLO 320DM (IC₅₀ = 84.68 μM), human testicular cancer NTERA-Scl-D1 (IC₅₀ = 1.44 μM) and human liver carcinoma SK-HEP-1 cells (IC₅₀ = 17.18 μM). Compound was also active against resistant cancer cell lines such as murine leukemia L1210 cells and human non-small cell lung cancer NCI-H460 cells (IC₅₀ = 12.96 and 20.41 μM, respectively). The cytotoxic activity of compound may be due to two distinct mechanisms: inhibition of protein phosphatase PP2A by release of demethylcantharidin and by platination of DNA. *In vivo*, compound produced tumor retardation and regression in nude mice bearing liver SK-HEP-1 carcinoma. Another related complex is:



303766: C₈ H₁₄ N₂ O₅ Pt

SOURCES – Chinese Academy of Sciences, Beijing (CN); Chinese University of Hong Kong, Sha Tin, HK (CN).

REFERENCES

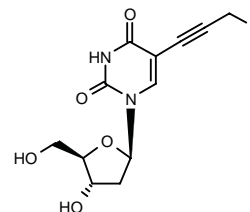
1. Au-Yeung, S.C.F. et al. (Chinese University of Hong Kong) *Synthesis of platinum complexes and uses thereof*. WO 9849174.
2. Ho, Y.-P. et al. *Potential new antitumor agents from an innovative combination of demethylcantharidin, a modified traditional Chinese medicine, with a platinum moiety*. J Med Chem 2001, 44(13): 2065.

ANTIMETABOLITES

FPdUrd

301687

5-(3-Fluoro-1-propynyl)-2'-deoxyuridine



C₁₂ H₁₃ F N₂ O₅; Mol wt: 284.2417

ACTION – Antineoplastic agent that acts by inhibiting thymidylate synthase (dTMP synthase) in a rapid and irreversible manner, as demonstrated in an *in vitro* assay. In addition, it was shown to inhibit the growth of human chronic myelogenous leukemia K-562 and murine lymphocytic leukemia L1210 cells with IC₅₀ values of about 13 and 3 nM, respectively. A representative compound from a series of 5-propynylpyrimidine derivatives.

SOURCE – State University of New York, Buffalo, Buffalo, NY (US).

REFERENCES

1. Kalman, T.I. and Nie, Z. (State University of New York, Buffalo) *5-Propynylpyrimidine derivs. as cytotoxic enzyme inhibitors*. WO 0114345.

ANTIBIOTICS AND ALKALOIDS

LIPOSOMAL DOXORUBICIN

125945

Liposome-encapsulated doxorubicin citrate complex

Dox99+
NSC-620212
TLC-Dox99
TLC-D-99

ACTION – Anthracycline glycoside antineoplastic agent.

INDICATION – First-line treatment of metastatic breast cancer in combination with cyclophosphamide.

PRESENTATION – Powder and preadmixtures for concentrate for liposomal dispersion for i.v. infusion, containing 50 mg of doxorubicin hydrochloride as the active ingredient; each carton contains one vial of Myocet™ doxorubicin hydrochloride plus excipients (lactose, methyl parahydroxybenzoate), one vial of Myocet™ liposomes (egg phosphatidyl choline, cholesterol, citric acid, sodium chloride, water for injection) and one vial of Myocet™ buffer (sodium carbonate, water for injection).

PROPRIETARY NAME – Myocet (GB).

SOURCE – The Liposome Co. (Elan).

RECENT REFERENCES

1. Batist, G. *Improving the therapeutic index when using Myocet™ in the treatment of metastatic breast cancer*. Breast 2001, 10(Suppl. 2): 16.

2. Batist, G. et al. *Decreased cardiac toxicity by TLC D-99 (liposome encapsulated doxorubicin) vs. doxorubicin in a randomized trial of metastatic breast carcinoma (MBC)*. Proc Am Soc Clin Oncol 1998, 17: Abst 443.

3. Batist, G. et al. *Improved therapeutic index of TLC D-99 (liposome-encapsulated doxorubicin) compared to free doxorubicin in first-line treatment of metastatic breast cancer in patients who had received prior adjuvant doxorubicin*. Proc Am Soc Clin Oncol 2000, 19: Abst 405.

4. Batist, G. et al. *Phase III study of liposome-encapsulated doxorubicin (TLC D-99) versus doxorubicin (DOX) in combination with cyclophosphamide (CPA) in patients (pts.) with metastatic breast cancer (MBC)*. Proc Am Soc Clin Oncol 1999, 18: Abst 486.

5. Batist, G. et al. *Randomized phase III trials of Myocet (liposomal-encapsulated doxorubicin) vs. doxorubicin or epirubicin in first-line treatment of metastatic breast cancer*. Ann Oncol 2000, 11(Suppl. 4): Abst 1030.

6. Boyle, J.A. *Clinical studies with Evacet (TLC D-99) and doxorubicin (DOX) in patients with metastatic breast carcinoma (MBC)*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst CARB 064.

7. Chan, S. et al. *Phase III study of liposome-encapsulated doxorubicin (TLC D-99) and cyclophosphamide (CPA) vs. epirubicin (EPI) and CPA in first-line treatment of metastatic breast cancer (MBC)*. Eur J Cancer 1999, 35(Suppl. 4): Abst 1263.

8. Cheung, T.W. et al. *Phase II study of liposomal doxorubicin (TLC D-99) in the treatment of AIDS-related Kaposi's sarcoma (KS)*. Proc Am Soc Clin Oncol 1998, 17: Abst 162.

9. Erdkamp, F. et al. *Phase III study of TLC D-99 (liposome encapsulated doxorubicin) plus cyclophosphamide vs. epirubicin (EPI) plus cyclophosphamide (CPA) in patients with metastatic breast carcinoma (MBC)*. Proc Am Soc Clin Oncol 1999, 18: Abst 459.

10. Gutheil, J.C. *Challenges and advantages in the treatment of breast cancer*. 17th Chemother Found Symp Innov Cancer Chemother Tomorrow (Nov 3-6, New York) 1999, Abst 85.

11. Harris, L. et al. *Phase III study of TLC D-99 (liposome encapsulated doxorubicin) vs. free doxorubicin (DOX) in patients with metastatic breast carcinoma (MBC)*. Proc Am Soc Clin Oncol 1998, 17: Abst 474.

12. Iannitti, D. and Safran, H. *TLC D-99 can be safely administered to patients with advanced hepatobiliary carcinomas and severe hepatobiliary dysfunction*. Proc Am Soc Clin Oncol 2000, 19: Abst 1214.

13. Janoff, A.S. et al. *Evacet(TM) (TLC-D99): A molecular and clinical rationale*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst CARB 063.

14. Levine, A. et al. *Liposomal doxorubicin (TLC D99, Myocet) in combination with cyclophosphamide (C), vincristine (O) and prednisone (P) for aggressive non-Hodgkin's lymphomas (NHL)*. Ann Oncol 2000, 11(Suppl. 4): Abst 478P.

15. Levine, A.M. et al. *Liposomal doxorubicin (TLC D-99) in combination with cyclophosphamide, vincristine, and prednisone in the treatment of aggressive lymphomas*. Proc Am Soc Clin Oncol 2000, 19: Abst 161.

16. Marty, M. *Liposomal doxorubicin (Myocet™) and conventional anthracyclines: A comparison*. Breast 2001, 10(Suppl. 2): 28.

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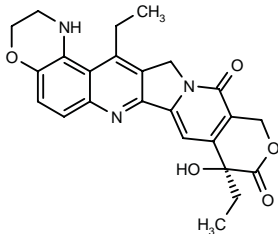
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DNA-INTERCALATING DRUGS

303076

9(S),16-Diethyl-9-hydroxy-1,2,3,9,12,15-hexahydro-10H,13H-pyrano[3'',4'':6',7']indolizino[2',1':5,6]-pyrido[3,2-f][1,4]benzoxazine-10,13-dione



C24 H23 N3 O5; Mol wt: 433.4617

ACTION – Antineoplastic agent, a camptothecin analogue with improved activity against topoisomerase I (IC₅₀ = 5 and 40 nM, respectively) and comparable cytotoxicity against a panel of human cancer cells including colon, lung, stomach, breast and ovarian carcinomas (IC₅₀ = 7-20 nM). Moreover, compound given at a dose of 10 mg/kg i.p. showed high antitumor activity in nude mice bearing colon cancer WiDr xenografts. Selected for further preclinical evaluation.

SOURCE – SK Chemicals.

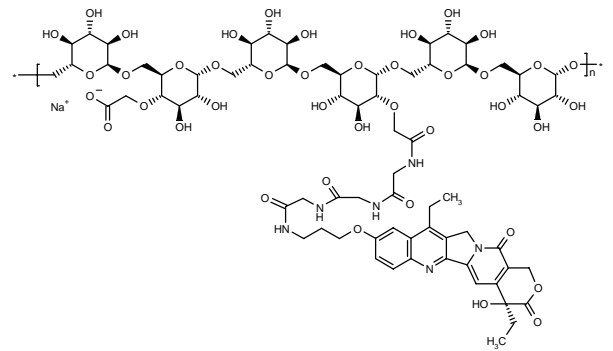
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T-0128

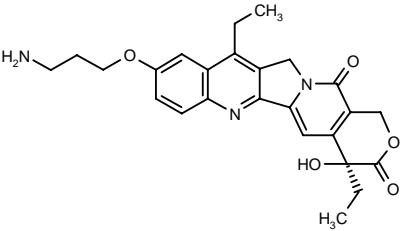
303086

Glycylglycyl-N-[3-[(4S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]-quinolin-9-yloxy]propyl]glycinamide compound with dextran carboxymethyl ether sodium salt



(C71 H97 N6 Na O41)n; Mol wt: 1713.5380

ACTION – Antineoplastic agent, a new prodrug consisting of the camptothecin analogue **T-2513** bound to carboxymethyl dextran through a triglycine spacer. The prodrug showed excellent *in vivo* efficacy, superior to irinotecan, against a panel of human tumor xenografts in nude mice including mammary carcinoma MX-1 (which was completely regressed after a single i.v. dose of 6 mg/kg), lung carcinoma LX-1, as well as gastric St-4 and human colon adenocarcinoma HT-29 cells highly resistant to camptothecins. Compound was also active in rats bearing Walker 256 carcinoma (ED₅₀ = 2.3 mg/kg i.v.). After i.v. administration, the prodrug was seen to accumulate in tumors where sustained release of the active compound was found.



T-2513 [304073]: C25 H27 N3 O5

SOURCE – Tanabe Seiyaku.

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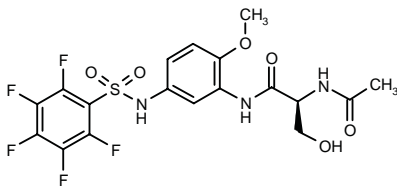
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ANTIMITOTIC DRUGS

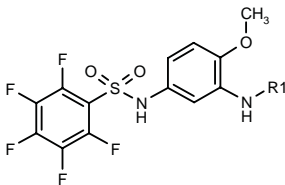
301557

N-Acetyl-L-serine 2-methoxy-5-(pentafluorophenylsulfonamido)phenylamide



C18 H16 F5 N3 O6 S; Mol wt: 497.3954

ACTION – Agent for the treatment of hyperproliferative disorders and disorders characterized by abnormally high levels of LDL or cholesterol such as cancer, bacterial infections, psoriasis, vascular restenosis, hypercholesterolemia and atherosclerosis that exhibits anti-proliferative activity by interacting with cellular tubulin and which also regulates LDL receptor gene expression. *In vitro*, compound was shown to produce total growth inhibition of human cervical adenocarcinoma HeLa cells at a concentration of 0.07 µM. Other exemplified compounds from this series of arylsulfonanilide derivatives include the following:



Compound	R1	Formula
301558	H-L-Ser-	C ₁₆ H ₁₄ F ₅ N ₃ O ₆ S
301560	H-Gly	C ₁₅ H ₁₂ F ₅ N ₃ O ₄ S
301562	Ac-Gly	C ₁₇ H ₁₄ F ₅ N ₃ O ₅ S
301564	Ac-L-Thr-	C ₁₉ H ₁₈ F ₅ N ₃ O ₆ S
301566	Ac-L-Asp-	C ₁₉ H ₁₆ F ₅ N ₃ O ₇ S
301568	Ac-β-Ala	C ₁₈ H ₁₆ F ₅ N ₃ O ₅ S
301569	H-L-Ala-	C ₁₆ H ₁₄ F ₅ N ₃ O ₄ S
301570	H-D-Ala-	C ₁₆ H ₁₄ F ₅ N ₃ O ₄ S
301571	Ac-D-Ala-	C ₁₈ H ₁₆ F ₅ N ₃ O ₅ S

SOURCE – Tularik.

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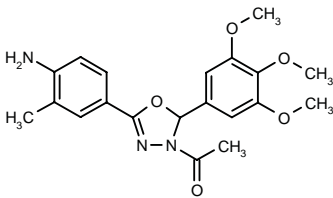
1. Rubenstein, S.M. and Jaen, J.C. (Tularik Inc.) *Arylsulfonanilide derivs*. WO 0112593.

A-105972

274502

4-[4-Acetyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]-2-methylphenylamine

3-Acetyl-5-(4-amino-3-methylphenyl)-2,3-dihydro-2-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole



C20 H23 N3 O5; Mol wt: 385.4177

ACTION – Potential antineoplastic agent proven to strongly inhibit the growth of human breast, CNS, colon, liver, lung and prostate cancer cell lines including multidrug-resistant cells, with IC₅₀ values of 20-200 nM. Compound was found to block the cell cycle at the G2/M phase, to bind to purified tubulin, to inhibit microtubule assembly *in vitro* and to induce apoptosis, possibly via inactivation of bcl-2. In studies in mice bearing melanoma B16, leukemia P388 and doxorubicin-resistant leukemia P388, compound was found to prolong life span at doses of 25-50 mg/kg/day i.p.

SOURCE – Abbott.

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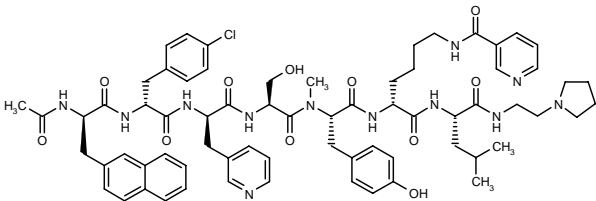
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HORMONAL AGENTS

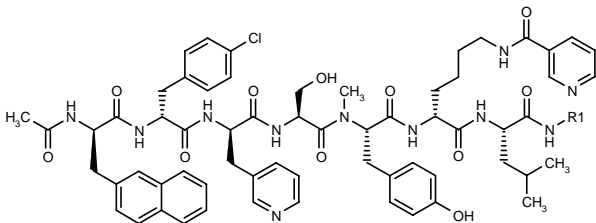
300786

N-Acetyl-3-(2-naphthyl)-D-alanyl-(4-chloro)-D-phenyl-alanyl-3-(3-pyridyl)-D-alanyl-L-seryl-N-methyl-L-tyrosyl-N⁶-(pyridin-3-ylcarbonyl)-D-lysyl-L-leucine N-[2-(1-pyrrolidinyl)ethyl]amide



C69 H85 Cl N12 O11; Mol wt: 1293.9570

ACTION – LHRH antagonist, as demonstrated in a rat pituitary receptor binding assay ($pA_2 = 11.27$) , potentially useful for the treatment of sex hormone-related disorders including precocious puberty, benign prostatic hyperplasia, breast and ovarian tumors, prostate tumors, hirsutism, gastric motility disorders, dysmenorrhea and endometriosis. Other compounds from this series of C-terminus modified heptapeptide LHRH analogues are:



Compound	R1	Formula
300787	i-PrNHCH2CH2	C ₆₈ H ₈₅ ClN ₁₂ O ₁₁
300788	i-PrNH(CH2)5	C ₇₁ H ₉₁ ClN ₁₂ O ₁₁
300789	(CH2)4NHC(=NH)NH2	C ₆₈ H ₈₅ ClN ₁₄ O ₁₁
300790	3-quinuclidinyl	C ₆₉ H ₈₃ ClN ₁₂ O ₁₁

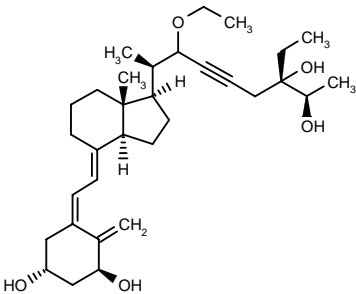
SOURCE – Abbott.

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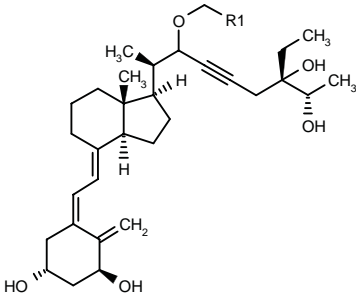
301115

20(R)-[(5*S*,6*R*)-1-Ethoxy-5-ethyl-5,6-dihydroxy-2-heptynyl]-1(*S*),3(*R*)-dihydroxy-9,10-secopregna-5(*Z*),7(*E*)-10(19)-triene



C₃₂H₅₀O₅; Mol wt: 514.7420

ACTION – Vitamin D analogue with antiproliferative, immunomodulating and antiinflammatory activities. Compared to prior art vitamin D analogues, this compound has reduced calcemic activity, much higher metabolic stability and only slightly reduced antiproliferative activity. It exhibited $-\log IC_{50}$ values of 8.9 ± 0.2 and 9.8 ± 0.2 in leukemia U-937 and mammary MCF-7 cancer cell assays, respectively, and was also active in a psoriasis model. Other exemplified compounds are:



Compound	R1	Formula
301119	H	C ₃₁ H ₄₈ O ₅
301120	Me	C ₃₂ H ₅₀ O ₅

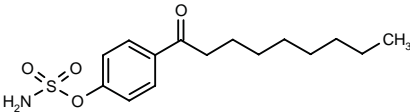
SOURCE – Leo.

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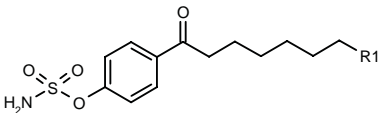
302717

Sulfamic acid 4-nonanoylphenyl ester



C₁₅H₂₃N O₄ S; Mol wt: 313.4157

ACTION – Estrone sulfatase inhibitor ($IC_{50} = 3.4 \mu M$) proven to be 3.5-fold more potent than COUMATE and 6.8-fold weaker than EMATE. Potentially useful for hormone-dependent breast cancer. Within this series of simple 4-sulfamated phenylalkylketones, the following are also described:



Compound	R1	Formula
302715	H	C ₁₃ H ₁₉ NO ₄ S
302716	Me	C ₁₄ H ₂₁ NO ₄ S

SOURCE – Kingston University, Kingston upon Thames (GB).

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CANCER IMMUNOTHERAPY

ALEMTUZUMAB

Prop INN

130761

Immunoglobulin G₁ (human–rat monoclonal CAMPATH-1H γ_1 -chain anti-human antigen CD52), disulfide with human–rat monoclonal CAMPATH-1H light chain, dimer

CAMPATH-1H⁺
LDP-03

ACTION – Recombinant DNA-derived humanized mono-clonal antibody directed against CD52 antigen.

INDICATION – Treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL) who have been treated with alkylating agents and have failed fludarabine therapy.

PRESENTATION – Single-use ampoules containing 30 mg of alemtuzumab in 3 ml solution.

PROPRIETARY NAME – Campath (US).

SOURCES – Millenium & Ilex Partners; marketed by Berlex.

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⁺Drug data Rep 1987, 009(04): 0350.

PEPTIDE LEUCINE ARGININE

303597

L-Leucyl-L-valyl-L-arginyl-glycyl-L-cysteinyl-L-tryptophyl-L-threonyl-L-lysyl-L-seryl-L-tyrosyl-L-prolyl-L-prolyl-L-lysyl-L-prolyl-L-cysteinyl-L-phenylalanyl-L-valyl-L-arginine cyclic S-3.5-S-3.15-disulfide

pLR

C99 H151 N27 O22 S2; Mol wt: 2135.5810

ACTION – Potent immunomodulatory peptide isolated from the skin of the Northern leopard frog, *Rana pipiens*. This peptide was found to elicit rapid and noncytotoxic histamine release from the rat peritoneal mast cells (EC_{50} = 330 nM), and was about 2-fold more potent than melittin, one the most active histamine-liberating peptides. The compound also inhibited granulocyte–macrophage colony formation, with no effect on apoptosis of mature neutrophils. In addition, the peptide showed potent antiproliferative effects mediated by specific binding sites expressed on ovarian breast cancer cell lines. Potentially useful as a chemotherapeutic agent.

SOURCE – Novo Nordisk.

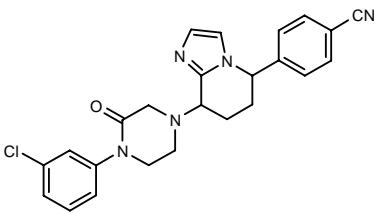
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

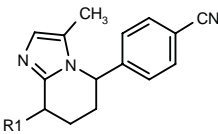
300722

4-[8-[4-(3-Chlorophenyl)-3-oxopiperazin-1-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-5-yl]benzonitrile



C24 H22 Cl N5 O; Mol wt: 431.9248

ACTION – Agent for the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed bicyclic compounds are:



Compound	R1	Formula
300723	4-(3-Cl-Ph)-3-oxo-1-Piz	C ₂₅ H ₂₄ ClN ₅ O
300724	NHCH2CH2CH(Ph)2	C ₃₀ H ₃₀ N ₄
300725	N[(CH2)3Ph]CH2CH2CH(Ph)2	C ₃₉ H ₄₀ N ₄
300726	NHCH(Ph)CH2CH2Ph	C ₃₀ H ₃₀ N ₄
300727	3-MeO-PhCH(Ph)CH2CH2NH	C ₃₁ H ₃₂ N ₄ O
300728	NH(CH2)3Ph	C ₂₄ H ₂₆ N ₄
300729	NH(CH2)4Ph	C ₂₅ H ₂₈ N ₄
300730	NHCO2CH2Ph	C ₂₃ H ₂₂ N ₄ O ₂
300731	NHCOCH2CH(Ph)2	C ₃₀ H ₂₈ N ₄ O
300732	3-(PhO)-PhCONH	C ₂₈ H ₂₄ N ₄ O ₂

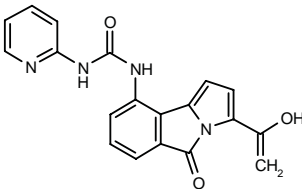
SOURCE – Merck & Co.

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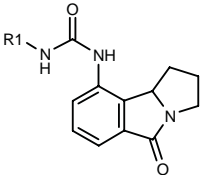
300823^{1,2}

1-[3-(1-Hydroxyvinyl)-5-oxo-5H-pyrrolo[2,1-a]isoindol-9-yl]-3-(2-pyridyl)urea



C19 H14 N4 O3; Mol wt: 346.3446

ACTION – Antineoplastic agent, an inhibitor of cyclin-dependent kinase 4 (CDK-4) and cyclin-dependent kinase 6 (CDK-6), as demonstrated *in vitro* by IC_{50} values of 0.061, 0.019 and 0.013 μ M, respectively, against purified D1/CDK-4, D2/CDK-4 and D1/CDK-6. In addition, it was shown to inhibit the proliferation of human colon carcinoma HCT 116 and human gastric carcinoma MKN-1 cells (IC_{50} = 0.013 and 0.10 μ M, respectively), being more potent than (\pm)-flavopiridol (IC_{50} = 0.15 and 0.87 μ M, respectively). Other exemplified compounds from this series of biarylurea derivatives include the following:



Compound	R1	Formula
300824	4-[1-(PhCH2)-3-pyrrolidinyl]-2-Pyr	C ₂₈ H ₂₉ N ₅ O ₂
300825	4-(BuNHCH2CH2)-2-Pyr	C ₂₃ H ₂₉ N ₅ O ₂
300826	5-(5-Cl-2-indanyl-NHCH2)-3-pyrazolyl	C ₂₅ H ₂₅ ClN ₆ O ₂

SOURCE – Banyu.

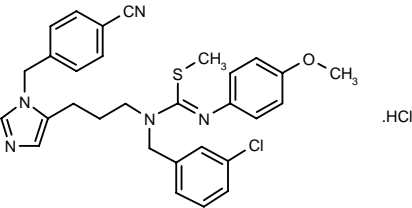
REFERENCES

1. Hayama, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Biarylurea derivs.* JP 2001106673, WO 0107411.

2. Honna, T. et al. *Structure-based design of potent CDK4 selective inhibitor.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 136.

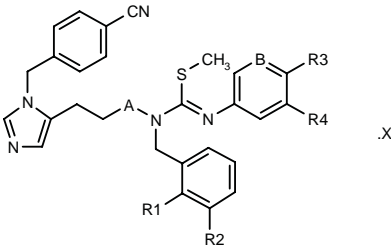
300970

*N*¹-(3-Chlorobenzyl)-*N*¹-[3-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]propyl]-*N*³-(4-methoxyphenyl)-*S*-methylisothiurea hydrochloride

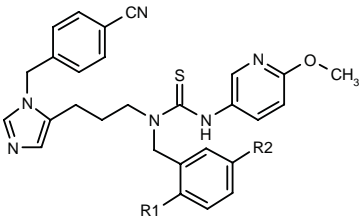


C30 H30 Cl N5 O S . HCl; Mol wt: 580.5809

ACTION – Antineoplastic agent that inhibits *K-ras* prenylation and the growth of *ras*-transformed cells. *In vitro*, compound was shown to inhibit protein farnesyl-transferase (IC₅₀ = 0.20 nM), as well as *K-ras*4B processing in NIH3T3 cells transfected with human *K-ras*4B (IC₅₀ = 360 nM). Other exemplified compounds from this series of thiourea and isothiurea derivatives include the following:



Compound	R1	R2	R3	A	B	X	Formula
300972	Cl	Cl	OMe	CH2	N		C ₂₉ H ₂₈ Cl ₂ N ₆ OS
300973	CF3	H	OMe	bond	N	2HCl	C ₂₉ H ₂₇ F ₃ N ₆ OS.2HCl
300975	H	Cl	H	CH2	C(F)		C ₂₉ H ₂₇ ClFN ₅ S
300976	Cl	Cl	OMe	bond	N	2HCl	C ₂₈ H ₂₆ Cl ₂ N ₆ OS.2HCl
300977	H	Cl	OMe	CH2	N	2HCl	C ₂₉ H ₂₉ ClN ₆ OS.2HCl



Compound	R1	R2	Formula
300971	CF3	H	C ₂₉ H ₂₇ F ₃ N ₆ OS
300974	H	Cl	C ₂₈ H ₂₇ ClN ₆ OS

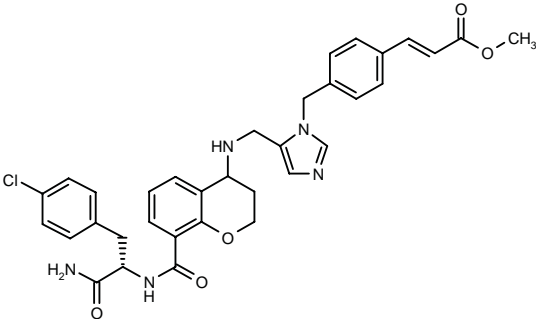
SOURCE – Yuhan.

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1. Lee, B.Y. et al. (Yuhan Corp.) *Thiourea and isothiurea derivs. for inhibiting ras-transformed cell growth.* WO 0109128.

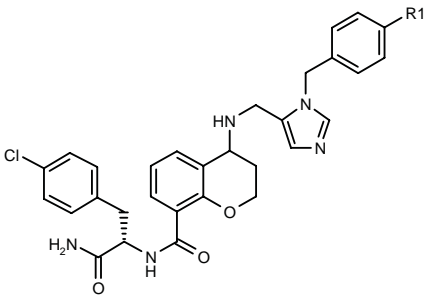
301000

3-[4-[5-[8-[*N*-(2-Amino-1(*S*)-(4-chlorobenzyl)-2-oxo-ethyl]carbamoyl]-3,4-dihydro-2*H*-1-benzopyran-4-ylaminomethyl]-1*H*-imidazol-1-ylmethyl]phenyl]-2-propenoic acid methyl ester



C34 H34 Cl N5 O5; Mol wt: 628.1256

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds from this series of 8-carbonyl chroman derivatives include the following:



Compound	R1	Formula
301001	CH2CH2CO2Me	C ₃₄ H ₃₆ ClN ₅ O ₅
301002	CH2CH2CONH2	C ₃₃ H ₃₅ ClN ₅ O ₄
301003	CH=CHCONH2	C ₃₃ H ₃₃ ClN ₅ O ₄
301004	(CH2)3OH	C ₃₃ H ₃₆ ClN ₅ O ₄

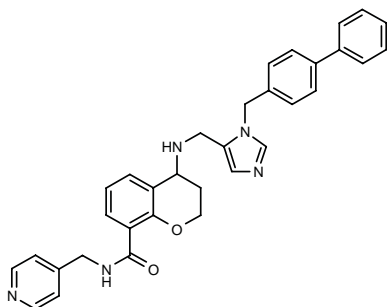
SOURCE – Aventis Pharma.

REFERENCES

1. Baudoin, B. et al. (Aventis Pharma SA) *Novel 8-carbonyl chroman derivs., preparation and therapeutic use thereof.* FR 2796948, WO 0109112.

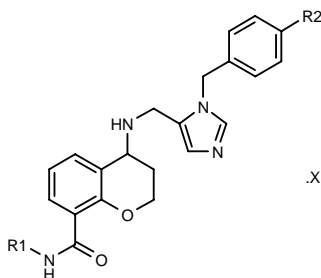
301005

(+)-4-[1-(Biphenyl-4-ylmethyl)-1*H*-imidazol-5-ylmethylamino]-*N*-(pyridin-4-ylmethyl)-3,4-dihydro-2*H*-1-benzopyran-8-carboxamide



C33 H31 N5 O2; Mol wt: 529.6409

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds from this series of 8-carbonyl chroman derivatives include the following:



Compound	R1	R2	X	Formula
301006	(S)-4-Cl-PhCH ₂ CH(Ac)	Me		C ₃₂ H ₃₃ ClN ₄ O ₃
301007	cyclohexyl-CH ₂	Ph		C ₃₄ H ₃₈ N ₄ O ₂
301011	(CH ₂) ₆ OH	Ph		C ₃₃ H ₃₈ N ₄ O ₃
301012	(S)-3-CF ₃ -PhCH(CH ₂ OH)	Ph		C ₃₆ H ₃₃ F ₃ N ₄ O ₃
301014	4-Cl-PhCH(CH ₂ CH ₂ OH)	Ph		C ₃₆ H ₃₅ ClN ₄ O ₃
301016	4-Pip-CH ₂	2-Me-Ph	3HCl	C ₃₄ H ₃₉ N ₅ O ₂ ·3HCl
301018	4-Pyr-CH ₂	2-NO ₂ -Ph		C ₃₃ H ₃₀ N ₆ O ₄

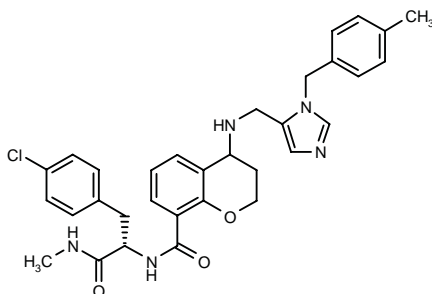
SOURCE – Aventis Pharma.

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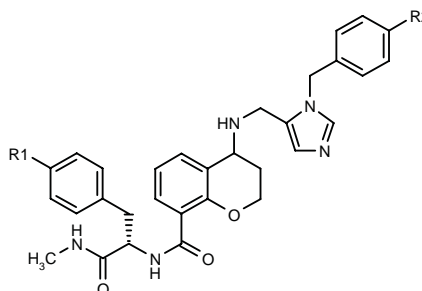
301019

N-[1(*S*)-(4-Chlorobenzyl)-2-(methylamino)-2-oxoethyl]-4-[1-(4-methylbenzyl)-1*H*-imidazol-5-ylmethylamino]-3,4-dihydro-2*H*-1-benzopyran-8-carboxamide



C32 H34 Cl N5 O3; Mol wt: 572.1056

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds from this series of 8-carbonyl chroman derivatives include the following:



Compound	R1	R2	Formula
301020	Cl	Br	C ₃₁ H ₃₁ BrClN ₅ O ₃
301021	Cl	CH ₂ CH ₂ CONH ₂	C ₃₄ H ₃₇ ClN ₆ O ₄
301022	Cl	5-oxazolyl	C ₃₄ H ₃₃ ClN ₆ O ₄
301023	Cl	5-pyrimidinyl	C ₃₅ H ₃₄ ClN ₇ O ₃
301024	Br	5-thiazolyl	C ₃₄ H ₃₃ BrN ₆ O ₃ S
301025	OH	5-thiazolyl	C ₃₄ H ₃₄ N ₆ O ₄ S

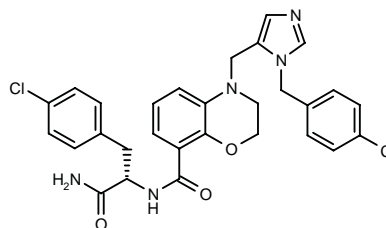
SOURCE – Aventis Pharma.

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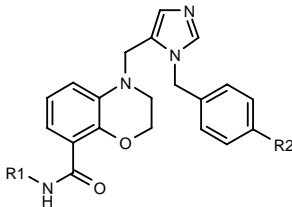
301026

N-[1(S)-Carbamoyl-2-(4-chlorophenyl)ethyl]-4-[1-(4-chlorobenzyl)-1*H*-imidazol-5-ylmethyl]-3,4-dihydro-2*H*-1,4-benzoxazine-8-carboxamide



C₂₉ H₂₇ Cl₂ N₅ O₃; Mol wt: 564.4703

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds from this series of 8-carbonyl benzoxazine derivatives include the following:



Compound	R1	R2	Formula
301027	(S)-4-MeO-PhCH2CH(CONH2)	Ph	C ₃₆ H ₃₅ N ₅ O ₄
301028	4-Pyr-CH2CH2	Cl	C ₂₇ H ₂₆ ClN ₅ O ₂
301029	(S)-CH(CH2OH)CH2CH2SMe	Cl	C ₂₅ H ₂₉ ClN ₄ O ₃ S
301030	3-MeO-PhCH2CH2	Cl	C ₂₉ H ₂₉ ClN ₄ O ₃
301031	4-Pyr-CH2	Ph	C ₃₂ H ₂₉ N ₅ O ₂
301032	4-Cl-2-F-PhCH2CH2	Cl	C ₂₈ H ₂₅ Cl ₂ FN ₄ O ₂
301034	(S)-C(Me)(CH2OH)CH2Ph	Cl	C ₃₀ H ₃₁ ClN ₄ O ₃

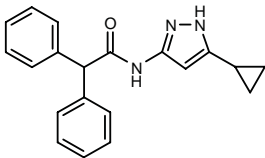
SOURCE – Aventis Pharma.

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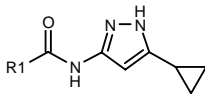
301387

N-(5-Cyclopropyl-1H-pyrazol-3-yl)-2,2-diphenylacetamide

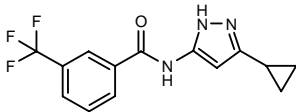


C20 H19 N3 O; Mol wt: 317.3901

ACTION – Antitumor agent with cyclin-dependent kinase (CDK)-inhibitory activity. This compound is also useful for the treatment of other proliferative disorders such psoriasis, vascular smooth muscle proliferation associated with atherosclerosis and postsurgical stenosis and restenosis, as well as in the treatment of Alzheimer’s disease. Other specifically claimed 3(5)-aminopyrazole derivatives include the following:



Compound	R1	Formula
301388	2-adamantyl	C ₁₇ H ₂₃ N ₃ O
301391	4-[4-(MeNHCH2)-Ph]-PhCH2	C ₂₂ H ₂₄ N ₄ O
301394	4-(4-Pr-Ph)-PhCH2	C ₂₃ H ₂₅ N ₃ O
301395	2-(AcNH)-PhCH2	C ₁₆ H ₁₈ N ₄ O ₂
301396	1-Ph-cyclopropyl	C ₁₆ H ₁₇ N ₃ O
301397	(S)-4-(1-oxo-2,3-dihydro-2-isoindolyl)-PhCH(Me)	C ₂₃ H ₂₂ N ₄ O ₂
301398	4-[3,4-(MeO)2-Ph]-PhCH2	C ₂₂ H ₂₃ N ₃ O ₃
301399	4-(3-AcO-5-indolyl)-PhCH2	C ₂₄ H ₂₂ N ₄ O ₃
301400	4-(4-dibenzofuryl)-PhCH2	C ₂₆ H ₂₁ N ₃ O ₂



301389: C14 H12 F3 N3 O

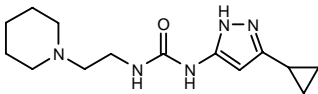
SOURCE – Pharmacia.

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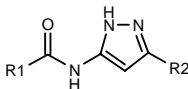
301403

N-(3-Cyclopropyl-1H-pyrazol-5-yl)-N’-[2-(1-piperidinyl)-ethyl]urea



C14 H23 N5 O; Mol wt: 277.3697

ACTION – Antitumor agent with cyclin-dependent kinase (CDK)-inhibitory activity. This compound is also useful for the treatment of other proliferative disorders such psoriasis, vascular smooth muscle proliferation associated with atherosclerosis and postsurgical stenosis and restenosis, as well as in the treatment of Alzheimer’s disease. Other specifically claimed 3(5)-ureidopyrazole derivatives include the following:



Compound	R1	R2	Formula
301404	5-MeO-3-indolyl-CH2CH2NH	cyclopropyl	C ₁₈ H ₂₁ N ₅ O ₂
301405	4-(1,3-benzodioxol-5-yl-CH2)-1-Piz	cyclopentyl	C ₂₁ H ₂₇ N ₅ O ₃
301407	4-(4-CF3-2-NO2-Ph)-1-Piz	cyclopentyl	C ₂₀ H ₂₃ F ₃ N ₆ O ₃
301410	NH(CH2)4OH	CH2CH2Ph	C ₁₆ H ₂₂ N ₄ O ₂
301411	3-Ac-PhNH	cyclopropyl	C ₁₅ H ₁₈ N ₄ O ₂
301412	NHPh	cyclopropyl	C ₁₃ H ₁₄ N ₄ O
301413	1,3-(Me)2-5-pyrazolyl-NH	cyclopropyl	C ₁₂ H ₁₆ N ₆ O
301414	4-OH-PhNH	cyclopropyl	C ₁₃ H ₁₄ N ₄ O ₂

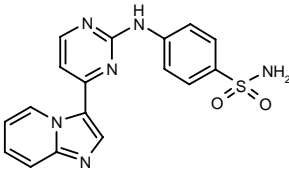
SOURCE – Pharmacia.

REFERENCES

1. Pevarello, P. et al. (Pharmacia & Upjohn SpA;Pharmacia Corp.) *3(5)-Ureido-pyrazole derivs., process for their preparation and their use as antitumor agents*. WO 0112188.

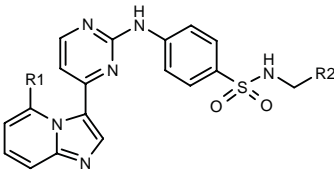
301777

4-[4-(Imidazo[1,2-*a*]pyridin-3-yl)pyrimidin-2-ylamino]-benzenesulfonamide



C17 H14 N6 O2 S; Mol wt: 366.4036

ACTION – An inhibitor of the cell cycle kinases CDK4, CDK6 and, especially, CDK2, potentially useful for the treatment of proliferative disorders such as cancer, as well as fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi’s sarcoma, hemangioma, acute and chronic nephropathies, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone disorders and ocular diseases with retinal vessel proliferation. Other specifically claimed compounds from this series of imidazo[1,2-*a*]pyridine and pyrazolo[2,3-*a*]pyridine derivatives are:



Compound	R1	R2	Formula
301778	H	H	C ₁₈ H ₁₆ N ₆ O ₂ S
301779	H	CH2OMe	C ₂₀ H ₂₀ N ₆ O ₃ S
301781	H	CH2CH2OMe	C ₂₁ H ₂₂ N ₆ O ₃ S
301782	H	i-PrNHCH2CH2	C ₂₃ H ₂₇ N ₇ O ₂ S
301783	H	CH2CH2N(Me)2	C ₂₂ H ₂₅ N ₇ O ₂ S
301784	H	CH2N(Me)2	C ₂₁ H ₂₃ N ₇ O ₂ S
301785	H	CH2NHMe	C ₂₀ H ₂₁ N ₇ O ₂ S
301786	SCH2CH2OH	CH2OMe	C ₂₂ H ₂₄ N ₆ O ₄ S ₂

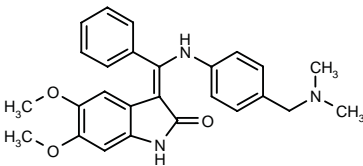
SOURCE – AstraZeneca.

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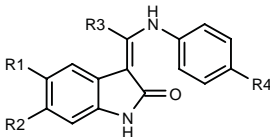
302022

(*Z*)-3-[1-[4-(Dimethylaminomethyl)phenylamino]-1-(phenyl)methylene]-5,6-dimethoxy-2,3-dihydro-1 *H*-indol-2-one



C26 H27 N3 O3; Mol wt: 429.5173

ACTION – An inhibitor of receptor tyrosine kinases such as VEGFR2, PDGFR α , PDGFR β , FGFR1, FGFR3, EGFR, HER2, IGF1R and HGFR, as well as cyclin/CDK complexes, which also inhibits the proliferation of endothelial cells and various tumor cells. *In vitro*, compound was found to inhibit the proliferation of human umbilical vein endothelial cells (HUVEC) with an IC₅₀ value of 0.02 μ M. LD₅₀ > 1000 mg/kg p.o. in mice. Other exemplified compounds from this series of substituted indolinones include the following:



Compound	R1	R2	R3	R4	Formula
302023	OMe	OMe	Ph	1-Pip-CH2	C ₂₉ H ₃₁ N ₃ O ₃
302024	OMe	OMe	Ph	CH2N(Me)CH2Ph	C ₃₂ H ₃₁ N ₃ O ₃
302025	OMe	OMe	Ph	N(Me)COCH2N(Me)2	C ₂₈ H ₃₀ N ₄ O ₄
302026	OMe	OMe	Ph	N(Ac)CH2CH2N(Me)2	C ₂₉ H ₃₂ N ₄ O ₄
302027	OMe	OMe	Ph	N(Ac)(CH2)3N(Me)2	C ₃₀ H ₃₄ N ₄ O ₄
302028	OMe	OMe	Et	N(Me)COCH2N(Me)2	C ₂₄ H ₃₀ N ₄ O ₄
302030	OMe	OMe	Ph	4-[N(Me)2CO]-1-Pip-CH2CH2	C ₃₃ H ₃₈ N ₄ O ₄
302031	H	NH2	Ph	1-Pip-CH2	C ₂₇ H ₂₈ N ₄ O

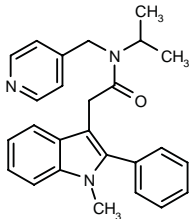
SOURCE – Boehringer Ingelheim.

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302038

N-Isopropyl-2-(1-methyl-2-phenyl-1 *H*-indol-3-yl)-*N*-(pyridin-4-ylmethyl)acetamide



C26 H27 N3 O; Mol wt: 397.5193

ACTION – Farnesyl pyrophosphate (FPP)-competitive farnesyltransferase inhibitor (IC₅₀ = 15 nM) inactive against K-Ras processing in PSN-1 cells (EC₅₀ > 30,000 nM) and geranylgeranyltransferase I. Potentially useful as an antineoplastic agent.

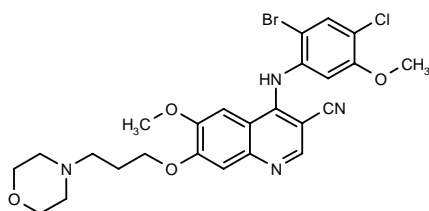
SOURCE – Merck & Co.

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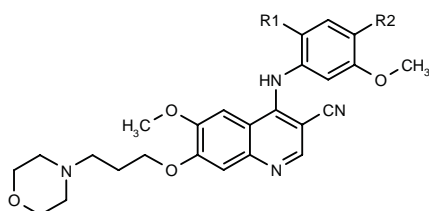
302048

4-(2-Bromo-4-chloro-5-methoxyphenylamino)-6-methoxy-7-[3-(4-morpholinyl)propoxy]quinoline-3-carbonitrile



C₂₅ H₂₆ Br Cl N₄ O₄; Mol wt: 561.8614

ACTION – Src protein tyrosine kinase inhibitor (IC₅₀ = 0.92 nM) with *in vitro* antiproliferative activity (IC₅₀ = 71 nM), potentially useful for the treatment of diseases characterized by increased Src expression such as cancer and osteoporosis. Within this series of 4-phenylamino-3-quinolinecarbonitriles, the following are also described:



Compound	R1	R2	Formula
302047	Cl	Cl	C ₂₅ H ₂₆ Cl ₂ N ₄ O ₄
302046	Br	H	C ₂₅ H ₂₆ BrClN ₄ O ₄

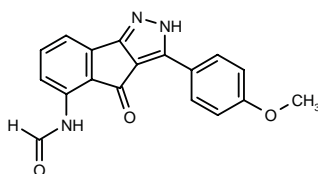
SOURCE – Wyeth-Ayerst.

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302656

N-[3-(4-Methoxyphenyl)-4-oxo-2,4-dihydroindeno[1,2-c]pyrazol-5-yl]formamide



C₁₈ H₁₃ N₃ O₃; Mol wt: 319.3187

ACTION – Antineoplastic agent, an inhibitor of cyclin-dependent kinase (IC₅₀ = 0.2 and 0.08 μM against CDK4/D1 and CDK2/E kinases, respectively) with *in vitro* cytotoxic activity against transformed colon cancer HCT 116 cells (IC₅₀ = 0.69 μM) but not against normal AG1523 fibroblasts (IC₅₀ > 63 μM). *In vivo* in a human xenograft model in mice, compound at 30 mg/kg i.p. for 14 days reduced tumor growth and increased survival, with an effect similar to flavopiridol.

SOURCE – DuPont Pharmaceuticals.

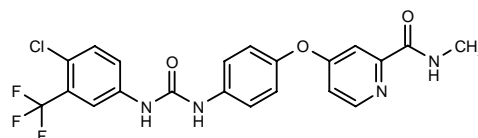
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BAY-43-9006

301618

4-[4-[3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido]-phenoxy]-N-methylpyridine-2-carboxamide



C₂₁ H₁₆ Cl F₃ N₄ O₃; Mol wt: 464.8294

ACTION – Orally active Raf kinase inhibitor (IC₅₀ = 12 nM) with broad antitumor efficacy both *in vitro* and *in vivo*. Compound inhibited MEK1 activation in B-raf ER 3T3 cells and phosphorylation of ERK1/2 in human colon carcinoma HCT 116 cells at concentrations that also inhibited proliferation of HCT 116 and human pancreatic tumor MIA PaCa-2 cells *in vitro*. *In vivo*, in nude mice bearing mutant K-Ras HCT 116, MIA PaCa-2 and lung NCI-H460 tumor xenografts, compound given at doses of 10-100 mg/kg p.o. produced dose-dependent inhibition of tumor growth (44-81%). In phase I clinical studies in patients with refractory solid tumors, compound showed favorable pharmacokinetics and safety.

SOURCES – Bayer; Onyx.

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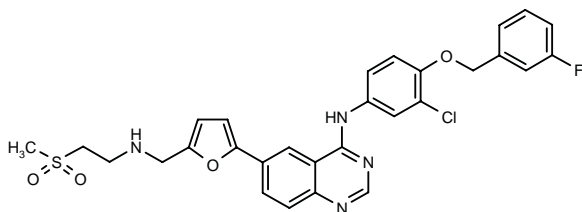
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GW-2016

301036

N-[3-Chloro-4-(3-fluorobenzyloxy)phenyl]-6-[5-[2-(methylsulfonyl)ethylaminomethyl]furan-2-yl]quinazolin-4-amine

GW-572016



C₂₉ H₂₆ Cl F N₄ O₄ S; Mol wt: 581.0654

ACTION – Antineoplastic agent, a potent, selective and reversible dual inhibitor of EGF receptor and ErbB-2 tyrosine kinase (IC₅₀ = 7.9 and 8 nM, respectively) with *in vitro* cytotoxic activity against human head and neck cancer HN5, breast carcinoma BT-474, lung adenocarcinoma Calu-3 and gastric cancer N87 cells that overexpress either the EGF receptor or ErbB-2 (IC₅₀ < 0.15 µM). Moreover, compound showed selectivity for cell lines expressing ErbB-2 versus Ha-ras and induced apoptosis in HN5, N87 and an SV40-transformed, ErbB-2-transfected breast epithelial cell line after several days' exposure. Compound exerts its antitumor effects by inhibiting ErbB-2 and EGF receptor activation via blockade of tyrosine autophosphorylation, leading to inhibition of downstream growth-promoting signaling pathways such as MAP kinase. *In vivo* in mice bearing ErbB-2-overexpressing ductal breast carcinoma BT-474 tumors, compound induced dose-dependent growth suppression, with 94% inhibition at a dose of 100 mg/kg b.i.d. for 21 days and 42% inhibition at the dose of 30 mg/kg; tumor regression was observed only at the higher dose. Almost complete inhibition of ErbB-2 phosphotyrosine levels was seen in tumors treated with the dose of 100 mg/kg. Similar results were obtained in mice bearing HN5 xenografts overexpressing the EGF receptor: a dose of 100 mg/kg b.i.d. for 21 days inhibited tumor growth by 101% and the lower dose of 30 mg/kg inhibited tumor growth by 34%. The tumor regression rate was > 25% and 18.7%, respectively.

SOURCE – GlaxoSmithKline.

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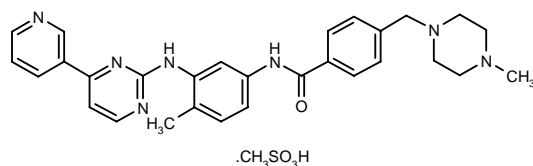
IMATINIB MESILATE

Prop INNM

229058

4-(4-Methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-[4-(3-pyridyl)pyrimidin-2-ylamino]phenyl]benzamide methane-sulfonate

GGP-57148B⁺
STI-571



C₂₉ H₃₁ N₇ O . C H₄ O₃ S; Mol wt: 589.7175

ACTION – Protein tyrosine kinase Bcr-Abl inhibitor.

INDICATION – Treatment of patients with chronic myeloid leukemia in blast crisis, accelerated phase or in chronic phase after failure of interferon alfa therapy.

PRESENTATION – Hard-gelatin capsules, equivalent to 100 mg imatinib.

PROPRIETARY NAME – *Gleevec* (US).

SOURCE – Novartis.

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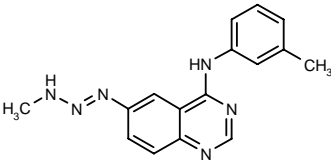
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SMA-41^{3,4}

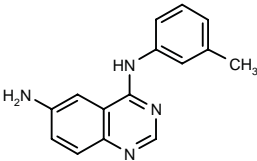
287418

N-(3-Methylphenyl)-6-(3-methyltriazen-1-yl)quinazolin-4-amine



C16 H16 N6; Mol wt: 292.3444

ACTION – Antineoplastic agent designed to release **SMA-52**, an inhibitor of epidermal growth factor receptor (EGFR) and methyldiazonium, a DNA-damaging agent. In A-431 cells, compound unlike SMA-52 alone, induced significant DNA damage and induced tyrosine phosphorylation and EGFR autophosphorylation in a concentration-dependent manner. Moreover, in A-431 cells, compound under continuous drug exposure (3-6 days) showed similar cytotoxicity to SMA-52; however, after short (2 h) drug exposure, SMA-52 showed almost complete loss of antiproliferative activity whereas compound retain almost 100% activity.



SMA-52 [215953]:^{*1-5} C15 H14 N4

SOURCE – McGill University, Montreal, PQ (CA).

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4. Matheson, S.L. et al. *Design of a chimeric 3-methyl-1,2,3-triazene with mixed receptor tyrosine kinase inhibitor with activity in a range of human tumour xenografts.* J Pharmacol Exp Ther 2001, 296(3): 832.

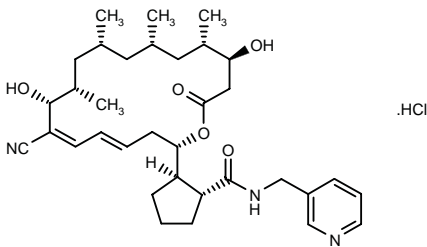
5. Woodburn, J.R. et al. *6-Amino-4-(3-methylphenylamino)-quinazoline: an EGF receptor tyrosine kinase inhibitor with activity in a range of human tumour xenografts.* Proc Amer Assoc Cancer Res 1996, 37: Abst 2665.

*Identified compound **215953** Drug Data Rep 1995, 017(08): 0769.

ANGIOGENESIS INHIBITORS

301035

(1*R*,2*R*)-2-[(2*S*,8*R*,9*S*,11*R*,13*S*,15*S*,16*S*)-7-Cyano-8,16-dihydroxy-9,11,13,15-tetramethyl-18-oxooxacycloocta-deca-4,6-dien-2-yl]-*N*-(pyridin-3-ylmethyl)cyclopentane-carboxamide hydrochloride



C34 H49 N3 O5 . HCl; Mol wt: 616.2380

ACTION – Agent for the treatment of cancer, arthritis, pannus and psoriasis with angiogenesis-inhibitory and antimetastatic activity. Compound was shown to significantly decrease the propagation of metastatic nodules in a Lewis lung adenocarcinoma model following i.p. or p.o. administration at one-fifth of the toxic dose, as well as to decrease the metastatic potential of murine colon 38 adenocarcinoma cells transplanted into the spleen at subtoxic doses.

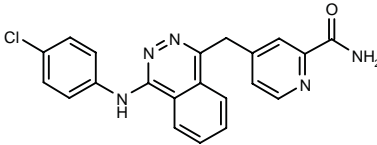
SOURCE – Gyogyszerkutato Intezet.

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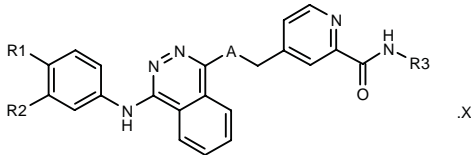
301223

4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridine-2-carboxamide



C21 H16 Cl N5 O; Mol wt: 389.8444

ACTION – Angiogenesis inhibitor that acts by inhibiting vascular endothelial growth factor receptor-2 (VEGFR-2, also known as kinase insert domain-containing receptor [KDR]). *In vitro*, compound was shown to inhibit KDR (IC₅₀ < 100 nM) and KDR phosphorylation in NIH3T3 cells (IC₅₀ < 20 nM). *In vivo*, compound was effective in a Matrigel angiogenesis model in mice, producing > 50% inhibition of the total hemoglobin content of Matrigel pellets at day 12 in animals that had been implanted s.c. with a mix of Matrigel and human SK-MEL-2 tumor cells when given at doses of 30, 100 and 300 mg/kg/day p.o. x 12 days. Potentially useful in the treatment of VEGF-mediated conditions such as tumor growth, retinopathy, rheumatoid arthritis, psoriasis and bullous disorder associated with subepidermal blister formation. Other exemplified compounds from this series of substituted pyridazines and fused pyridazines include the following:



Compound	R1	R2	R3	A	X	Formula
301224	H	Br	Me	bond		C ₂₂ H ₁₈ BrN ₅ O
301225	H	Br	H	bond		C ₂₁ H ₁₆ BrN ₅ O
301226	Cl	H	Me	bond	2HCl	C ₂₂ H ₁₈ ClN ₅ O.2HCl
301227	Cl	H	H	O	2HCl	C ₂₁ H ₁₆ ClN ₅ O ₂ .2HCl
301228	Cl	H	H	O	2MeSO3H	C ₂₁ H ₁₆ ClN ₅ O ₂ .2CH ₄ O ₃ S

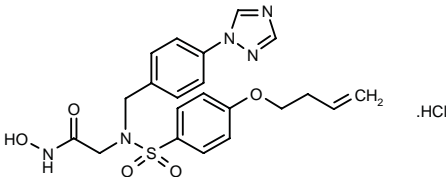
SOURCE – Bayer.

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1. Dumas, J.P. et al. (Bayer Corp.) *Substd. pyridazines and fused pyridazines with angiogenesis inhibiting activity.* WO 0110859.

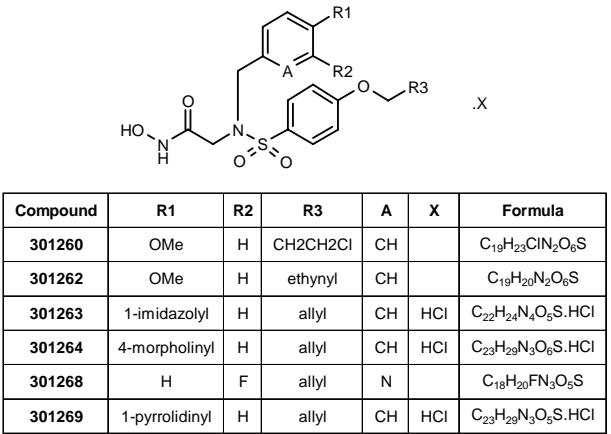
301258

2-[*N*-[4-(3-Butenyloxy)phenylsulfonyl]-*N*-[4-(1*H*-1,2,4-triazol-1-yl)benzyl]amino]acetohydroxamic acid hydrochloride



C21 H23 N5 O5 S . HCl; Mol wt: 493.9696

ACTION – An inhibitor of matrix metalloproteinases (MMP) with selectivity for MT1-MMP, MMP-2 and MMP-9 relative to MMP-1, potentially useful for the treatment of cancer and respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD). *In vitro*, compound gave IC₅₀ values of 0.0007, 5.850, 0.0002 and 0.0002 μM, respectively, against human MT1-MMP, MMP-1, MMP-2 and MMP-9. A representative compound from a series of arylsulfonamido-substituted hydroxamic acid derivatives, wherein the following compounds are also included:



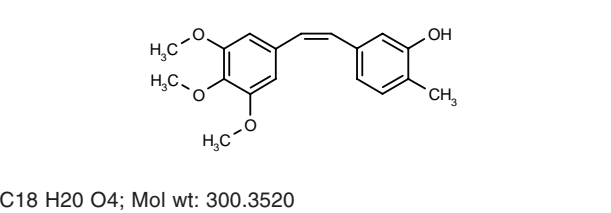
SOURCE – Novartis.

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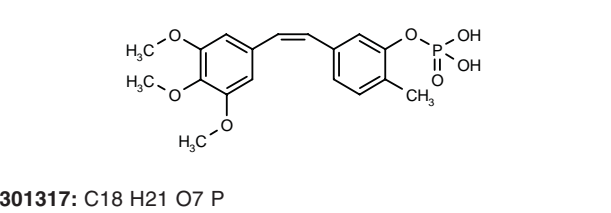
1. Breitenstein, W. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Arylsulfonamido-substd. hydroxamic acid derivs.* WO 0110827.

301316

2-Methyl-5-[(Z)-2-(3,4,5-trimethoxyphenyl)vinyl]phenol



ACTION – Vascular damaging agent that specifically damages newly formed vascular endothelium and is particularly useful for the treatment of solid tumors, as well as other diseases associated with neovascularization such as diabetic retinopathy, psoriasis, rheumatoid arthritis, macular degeneration and atherosclerosis. This compound reduced the functional vascular volume in CaNT tumor-bearing mice by 88% at 50 mg/kg i.p. Another specifically claimed *cis*-stilbene is:



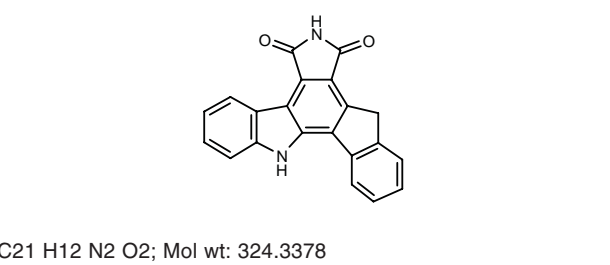
SOURCE – Angiogene Pharmaceuticals.

REFERENCES

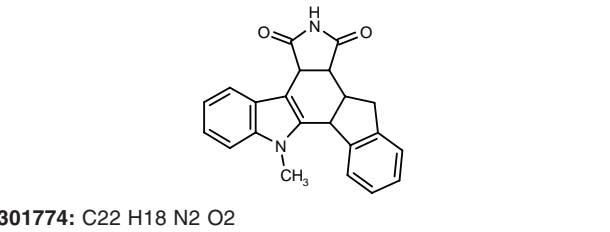
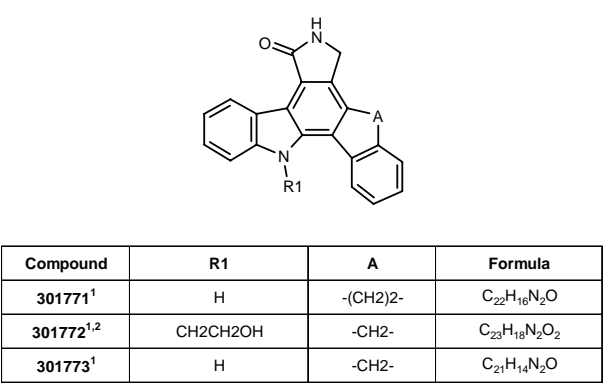
1. Davis, P.D. (Angiogene Pharmaceuticals Ltd.) *New stilbenes with vascular damaging activity.* WO 0112579.

301769¹

6,7,8,13-Tetrahydro-5*H*-indeno[1,2-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-dione



ACTION – Vascular endothelial growth factor receptor (VEGFR) kinase inhibitor (IC₅₀ = 71 nM) shown to be inactive against trkA kinase (0% inhibition at 300 nM) or platelet-derived growth factor receptor β (PDGFRβ) kinase (6% inhibition at 1 μM). Potentially useful for the treatment or prevention of angiogenic disorders and cancer. In addition, compound is reported to enhance the function and/or survival of trophic factor-responsive cells such as cholinergic neurons, and as such may be useful for treating various neurological disorders. Other exemplified compounds from this series of fused pyrrolocarbazoles and isoindolones with kinase-inhibitory activity include the following:



SOURCE – Cephalon.

REFERENCES

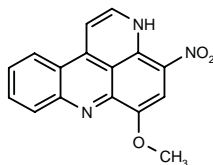
1. Hudkins, R.L. (Cephalon, Inc.) *Isomeric fused pyrrolocarbazoles and isoindolones.* WO 0114380.

2. Strum, M. et al. *Synthesis and SAR of new taxane reversal agents.* 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 131.

OTHER ONCOLYTIC DRUGS

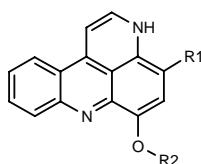
300877

6-Methoxy-4-nitro-3*H*-pyrido[2,3,4-*k*]acridine



C₁₆ H₁₁ N₃ O₃; Mol wt: 293.2809

ACTION – Antineoplastic agent with cytotoxicity against murine lymphoid neoplasm P388D1, human lung carcinoma A549, human colon carcinoma HT-29 and human melanoma SK-MEL-28 cell lines (IC₅₀ = 0.34, 0.03, 0.34 and 0.03 μM, respectively). Other specifically claimed compounds from this series of pyrido[2,3,4-*k*]acridine derivatives are:



Compound	R1	R2	Formula
300878	H	Me	C ₁₆ H ₁₂ N ₂ O
300879	H	H	C ₁₅ H ₁₀ N ₂ O
300880	NHAc	Me	C ₁₈ H ₁₅ N ₃ O ₂

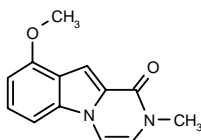
SOURCE – Universitat de Barcelona, Barcelona (ES).

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1. Alvarez, M. et al. (Universitat de Barcelona) *New cytotoxic pyrido[2,3,4-*k*]acridine derivs., their preparation and their therapeutic use*. WO 0109133.

300950

9-Methoxy-2-methyl-1,2-dihydropyrazino[1,2-*a*]indol-1-one



C₁₃ H₁₂ N₂ O₂; Mol wt: 228.2498

ACTION – Agent with antitumor activity, particularly active against colon and lung tumors. A representative compound from a series of 1,2-dihydro-1-oxopyrazino[1,2-*a*]indole derivatives.

SOURCE – Novuspharma.

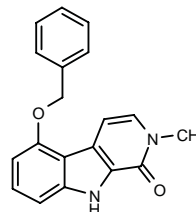
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300951

5-(Benzyloxy)-2-methyl-2,9-dihydro-1*H*-pyrido[3,4-*b*]indol-1-one

5-(Benzyloxy)-2-methyl-2,9-dihydro-1*H*-β-carbolin-1-one



C₁₉ H₁₆ N₂ O₂; Mol wt: 304.3474

ACTION – Antineoplastic agent particularly active against colon and lung tumors. A representative compound from a series of 1*H*-pyrido[3,4-*b*]indol-1-one derivatives.

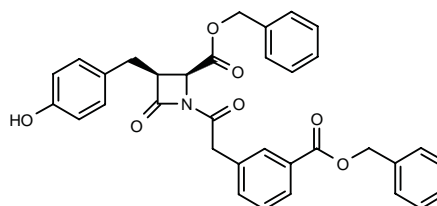
SOURCE – Novuspharma.

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1. Menta, E. et al. (Novuspharma SpA) *1*H*-Pyrido[3,4-*b*]indol-1-one derivs*. WO 0109129.

303075

1-[2-[3-(Benzyloxycarbonyl)phenyl]acetyl]-3(*S*)-(4-hydroxybenzyl)-4-oxoazetidine-2(*S*)-carboxylic acid benzyl ester



C₃₄ H₂₉ N O₇; Mol wt: 563.6031

ACTION – An inhibitor of prostate-specific antigen (PSA; IC₅₀ = 226 nM), potentially useful for the treatment of prostate cancer.

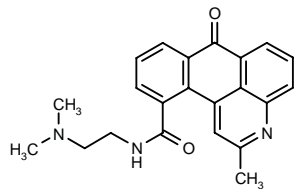
SOURCE – Lilly.

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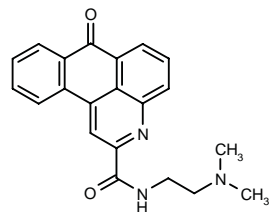
303691

N-[2-(Dimethylamino)ethyl]-2-methyl-7-oxo-7*H*-naphtho-[1,2,3-*de*]quinoline-11-carboxamide



C22 H21 N3 O2; Mol wt: 359.4269

ACTION – Cytotoxic agent with *in vitro* growth-inhibitory properties against murine leukemia P388 cells, Lewis lung carcinoma and Jurkat human leukemia cells (IC₅₀ = 100, 101 and 424 nM, respectively). *In vivo*, in mice bearing colon 38 tumors, compound given on an intermittent dose schedule (every 4 days x 3) at 30 and 45 mg/kg produced a 20-day growth delay, with complete regression at the higher dose. Another related compound is:



303688: C21 H19 N3 O2

SOURCES – University of Auckland, Auckland (NZ); La Trobe University, Bundoora (AU).

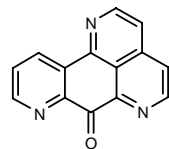
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1. Bu, X. et al. *Synthesis and cytotoxic activity of 7-oxo-7H-dibenz [f,ij]isoquinoline and 7-oxo-7H-benzo[e]perimidine derivatives*. J Med Chem 2001, 44(12): 2004.

CRL-8294

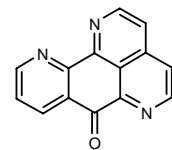
301318

7*H*-Pyrido[4,3,2-*de*][1,7]phenanthrolin-7-one



C14 H7 N3 O; Mol wt: 233.2293

ACTION – Antitumor agent with cytotoxicity against a panel of 12 human cell lines, giving a mean IC₅₀ value of 1450 nM. *In vivo*, compound was effective in inhibiting tumor growth in mice bearing hormone-insensitive and hormone-sensitive murine mammary carcinoma MXT-HI and MXT-HS tumors (36 and 64% inhibition at 5 mg/kg i.p., respectively). In addition, this compound was shown to prolong the life span of mice bearing L1210 lymphomas, giving a T/C x 100 value of 136% at 1.25 mg/kg i.p. The maximum tolerated dose (MTD) in mice was 10 mg/kg i.p. Another compound from this series of phenanthrolin-7-one derivatives is:



CRL-8293 [301319]: C14 H7 N3 O

SOURCE – Lafon.

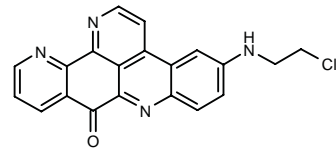
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CRL-8423

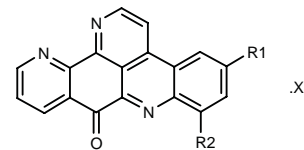
301320

5-(2-Chloroethylamino)-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one



C20 H13 Cl N4 O; Mol wt: 360.8027

ACTION – Antitumor agent with potent cytotoxicity against a panel of 12 human cell lines, giving a mean IC₅₀ value of 7 nM, while exhibiting low direct toxicity (maximum tolerated dose [MTD] > 160 mg/kg i.p. in mice). A representative compound from a series of ascididemin derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
CRL-8325 [301321]	N(Me)2	H		C ₂₀ H ₁₄ N ₄ O
CRL-8344 [301322]	H	NH2		C ₁₈ H ₁₀ N ₄ O
CRL-8347 [301323]	NH2	H		C ₁₈ H ₁₀ N ₄ O
CRL-8407 [301324]	N(Me)2	H	HCl	C ₂₀ H ₁₄ N ₄ O.HCl

SOURCE – Lafon.

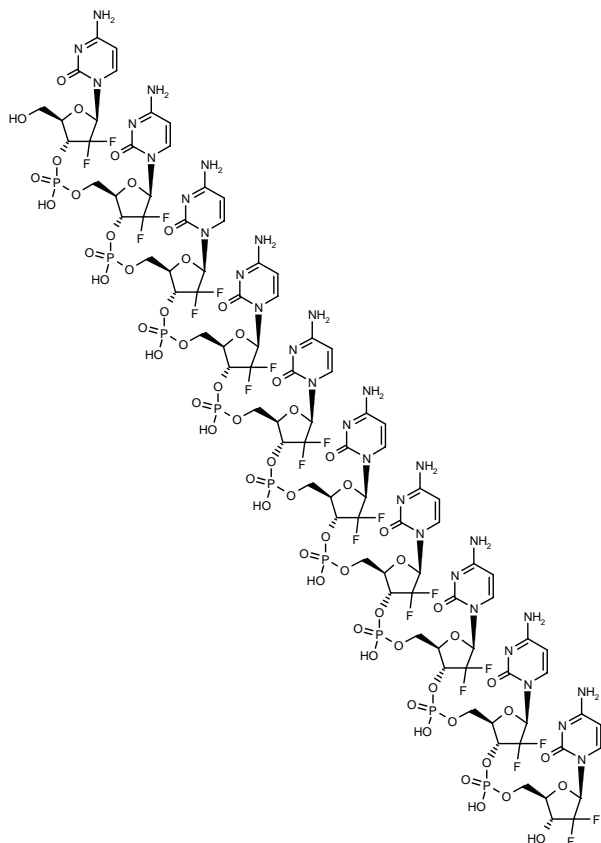
REFERENCES

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GEMMP[10]

302091

2'-Deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidylyl-(5'→3')-2'-deoxy-2',2'-difluorocytidine



C90 H101 F20 N30 O58 P9; Mol wt: 3189.6660

ACTION – Antineoplastic agent, a multimeric gemcitabine monophosphate prodrug with strong cytotoxicity against thyroid cancer cell lines (IC_{50} = 3.9-5.0 nM). Compound produced cell growth arrest in the S phase of the cell cycle, induced apoptosis after 12- or 24-h incubation and increased Fas expression in cultured thyroid cancer cell lines.

SOURCES – Johann Wolfgang Goethe Universität, Frankfurt (DE); Wake Forest University, Winston-Salem, NC (US).

REFERENCES

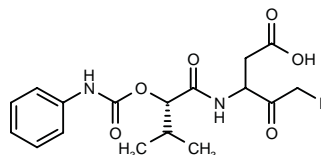
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2. Kotchetkov, R. et al. *Antineoplastic activity of a novel multimeric gemcitabine-monophosphate prodrug against thyroid cancer cells in vitro*. Anticancer Res 2000, 20(5A): 2915.

CHEMOPROTECTIVE AGENTS

301998

5-Fluoro-3-[3-methyl-2(*S*)-(N-phenylcarbamoyloxy)butyramido]-4-oxopentanoic acid



C17 H21 F N2 O6; Mol wt: 368.3589

ACTION – A representative compound from a series of substituted α -hydroxy acid derivatives that act as potent inhibitors of caspases and apoptotic cell death, and thus are expected to be useful for the treatment or amelioration of cell death in the central or peripheral nervous system, retinal neurons, cardiac muscle or immune system cells. Preferably, this compound may be used to treat, ameliorate or prevent cell death due to chemotherapy or radiation therapy. *In vitro*, compound was found to inhibit caspase 3 with an IC_{50} value of 17 nM. In addition, it was shown to block TNF- α -induced HeLa cell death with an EC_{50} value of 150 nM.

SOURCE – Cytovia.

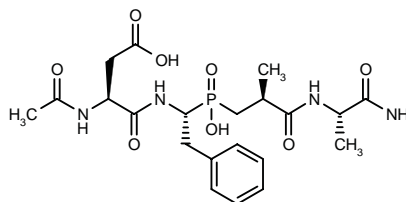
REFERENCES

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RXP-407*

285053

3(*S*)-Acetamido-4-[*N*-[1(*R*)-[[3-[1(*S*)-carbamoyl-ethyl-amino]-2(*S*)-methyl-3-oxopropyl](hydroxy)phosphoryl]-2-phenylethyl]amino]-4-oxobutyric acid



C21 H31 N4 O8 P; Mol wt: 498.4699

ACTION – Selective inhibitor of the N-domain of human angiotensin-converting enzyme (ACE), with a K_i value of 12 nM and a value about 3 orders of magnitude lower for the C-domain of the enzyme ($K_i = 25 \mu\text{M}$). Compound showed *in vivo* metabolic stability and a favorable pharmacokinetic profile, with plasma concentrations at 2 h after administration higher than the K_i value for inhibition N-domain of ACE. Compound significantly inhibited *ex vivo* plasma ACE N-domain activity and significantly blocked the *in vivo* degradation of protein AcSDPK, a negative regulator of hematopoietic stem cell differentiation and proliferation. No effect on blood pressure regulation was seen. Potentially useful for facilitating hematopoietic recovery after aggressive cancer therapy.

SOURCE – INSERM, Paris Cedex (FR).

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2. Coates, D. et al. *Functional conservation of the active sites of human and Drosophila angiotensin I-converting enzyme*. Biochemistry 2000, 39(30): 8963.

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4. Junot, C. et al. *RXP 407, a selective inhibitor of the N-domain of angiotensin I-converting enzyme, blocks in vivo the degradation of hemoregulatory peptide acetyl-Ser-Asp-Lys-Pro with no effect on angiotensin I hydrolysis*. J Pharmacol Exp Ther 2001, 297(2): 606.

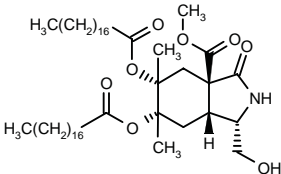
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*Identified compound **285053** Drug Data Rep 2000, 022(04): 0388.

OCULAR MEDICATIONS

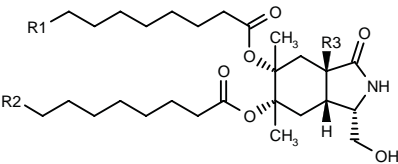
301501

(1*S*,3*aR*,5*R*,6*S*,7*aR*)-1-(Hydroxymethyl)-5,6-dimethyl-3-oxo-5,6-bis(stearoyloxy)perhydroisoindole-3*a*-carboxylic acid methyl ester



C49 H89 N O8; Mol wt: 820.2411

ACTION – Protein kinase C (PKC) activator (76.5% activation at 6 μM) with potential for the treatment of PKC-related disorders such as ocular hypertension, glaucoma, CNS disorders such as Alzheimer's disease and cancer. Other exemplified compounds from this series of azabicyclononane derivatives include the following:



Compound	R1=R2	R3	Formula
301502	Me	CO2Me	C ₃₃ H ₅₇ NO ₈
301503	vinyl	CO2Me	C ₃₅ H ₅₇ NO ₈
301504	(Z)-CH=CHC8H17	CO2Me	C ₄₉ H ₈₅ NO ₈
301505	Me	CH2OCOC9H19	C ₄₂ H ₇₅ NO ₈

SOURCE – Senju.

REFERENCES

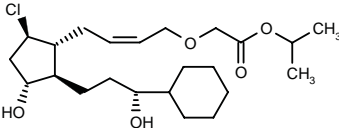
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AL-6598

303421

(5*Z*,9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoorprosta-5-enoic acid isopropyl ester

2-[4-[(1*R*,2*R*,3*R*,5*R*)-5-Chloro-2-[3(*R*)-cyclohexyl-3-hydroxypropyl]-3-hydroxycyclopentyl]-2(*Z*)-butenyloxy]-acetic acid isopropyl ester



C23 H39 Cl O5; Mol wt: 431.0091

ACTION – Prostaglandin DP receptor agonist potentially useful for the treatment of glaucoma. Compound showed an ocular hypotensive effect in monkeys with unilateral laser-induced glaucoma, where it significantly decreased intraocular pressure (IOP) in normotensive but not in hypertensive eyes. The hypotensive effect appeared to be attributable to an increase in uveoscleral outflow. In ocular hypertensive men, significant reductions in IOP (21.7-28.7%) were obtained with the dose of 0.01% twice daily. A combination of 0.012% compound and 0.2% brimonidine was effective in reducing IOP in hypertensive monkeys, and combination of 0.12% AL-6598 and 0.2% brimonidine b.i.d. was at least as effective as once-daily latanoprost and twice-daily timolol in reducing IOP in humans. Minimal hyperemia was seen in both guinea pigs and man treated with compound plus brimonidine.

SOURCE – Alcon.

REFERENCES

1. Salee, V.L. et al. (Alcon Laboratories, Inc.) *Use of certain prostaglandin analogues to treat glaucoma and ocular hypertension*. CA 2138181, EP 0667160, JP 1998120572, US 5807892.

2. Schneider, L.W. (Alcon Laboratories, Inc.) *Storage-stable prostaglandin compsns*. AU 4649596, EP 0812198, US 5631287, WO 9729752.

3. Weiner, A.L. et al. (Alcon Laboratories, Inc.) *Prostaglandin product*. WO 0003736.

ACTION – Selective inhibitor of the N-domain of human angiotensin-converting enzyme (ACE), with a K_i value of 12 nM and a value about 3 orders of magnitude lower for the C-domain of the enzyme ($K_i = 25 \mu\text{M}$). Compound showed *in vivo* metabolic stability and a favorable pharmacokinetic profile, with plasma concentrations at 2 h after administration higher than the K_i value for inhibition N-domain of ACE. Compound significantly inhibited *ex vivo* plasma ACE N-domain activity and significantly blocked the *in vivo* degradation of protein AcSDPK, a negative regulator of hematopoietic stem cell differentiation and proliferation. No effect on blood pressure regulation was seen. Potentially useful for facilitating hematopoietic recovery after aggressive cancer therapy.

SOURCE – INSERM, Paris Cedex (FR).

REFERENCES

1. Dive, V. et al. (Commissariat a l'Energie Atomique;INSERM [Institut National de la Sante et de la Recherche Medicale]) *N-Terminal site selective inhibitors of human angiotensin conversion enzyme (ACE)*. EP 1091966, WO 0001706.

2. Coates, D. et al. *Functional conservation of the actives sites of human and Drosophila angiotensin I-converting enzyme*. Biochemistry 2000, 39(30): 8963.

3. Dive, V. et al. *RXP 407, a phosphinic peptide, is a potent inhibitor of angiotensin I converting enzyme able to differentiate between its two active sites*. Proc Natl Acad Sci USA 1999, 96(8): 4330.

4. Junot, C. et al. *RXP 407, a selective inhibitor of the N-domain of angiotensin I-converting enzyme, blocks in vivo the degradation of hemoregulatory peptide acetyl-Ser-Asp-Lys-Pro with no effect on angiotensin I hydrolysis*. J Pharmacol Exp Ther 2001, 297(2): 606.

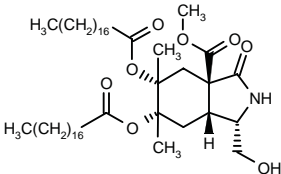
5. Vazeux, G. et al. *Potency and selectivity of RXP407 on human, rat, and mouse angiotensin-converting enzyme*. Biochem Pharmacol 2001, 61(7): 835.

*Identified compound **285053** Drug Data Rep 2000, 022(04): 0388.

OCULAR MEDICATIONS

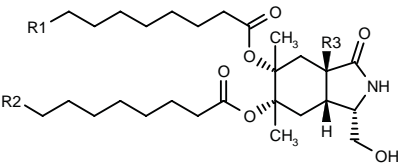
301501

(1*S*,3*aR*,5*R*,6*S*,7*aR*)-1-(Hydroxymethyl)-5,6-dimethyl-3-oxo-5,6-bis(stearoyloxy)perhydroisoindole-3*a*-carboxylic acid methyl ester



C49 H89 N O8; Mol wt: 820.2411

ACTION – Protein kinase C (PKC) activator (76.5% activation at 6 μM) with potential for the treatment of PKC-related disorders such as ocular hypertension, glaucoma, CNS disorders such as Alzheimer's disease and cancer. Other exemplified compounds from this series of azabicyclononane derivatives include the following:



Compound	R1=R2	R3	Formula
301502	Me	CO2Me	C ₃₃ H ₅₇ NO ₈
301503	vinyl	CO2Me	C ₃₅ H ₅₇ NO ₈
301504	(Z)-CH=CHC8H17	CO2Me	C ₄₉ H ₈₅ NO ₈
301505	Me	CH2OCOC9H19	C ₄₂ H ₇₅ NO ₈

SOURCE – Senju.

REFERENCES

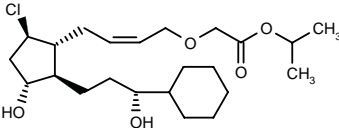
1. Sai, O. et al. (Senju Pharmaceuticals Co., Ltd.) *Azabicyclononane derivs. and their use*. JP 2001031649.

AL-6598

303421

(5*Z*,9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoorprosta-5-enoic acid isopropyl ester

2-[4-[(1*R*,2*R*,3*R*,5*R*)-5-Chloro-2-[3(*R*)-cyclohexyl-3-hydroxypropyl]-3-hydroxycyclopentyl]-2(*Z*)-butenyloxy]-acetic acid isopropyl ester



C23 H39 Cl O5; Mol wt: 431.0091

ACTION – Prostaglandin DP receptor agonist potentially useful for the treatment of glaucoma. Compound showed an ocular hypotensive effect in monkeys with unilateral laser-induced glaucoma, where it significantly decreased intraocular pressure (IOP) in normotensive but not in hypertensive eyes. The hypotensive effect appeared to be attributable to an increase in uveoscleral outflow. In ocular hypertensive men, significant reductions in IOP (21.7-28.7%) were obtained with the dose of 0.01% twice daily. A combination of 0.012% compound and 0.2% brimonidine was effective in reducing IOP in hypertensive monkeys, and combination of 0.12% AL-6598 and 0.2% brimonidine b.i.d. was at least as effective as once-daily latanoprost and twice-daily timolol in reducing IOP in humans. Minimal hyperemia was seen in both guinea pigs and man treated with compound plus brimonidine.

SOURCE – Alcon.

REFERENCES

1. Salee, V.L. et al. (Alcon Laboratories, Inc.) *Use of certain prostaglandin analogues to treat glaucoma and ocular hypertension*. CA 2138181, EP 0667160, JP 1998120572, US 5807892.

2. Schneider, L.W. (Alcon Laboratories, Inc.) *Storage-stable prostaglandin compsns*. AU 4649596, EP 0812198, US 5631287, WO 9729752.

3. Weiner, A.L. et al. (Alcon Laboratories, Inc.) *Prostaglandin product*. WO 0003736.

4. Hellberg, M.R. et al. *The clinical efficacy of AL-6598, DP prostaglandin analog, alone and in combination with brimonidine*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

5. Varnell, E.D. et al. *Effect of AL0-6598, a D-series prostaglandin, on severity and recurrences of herpetic keratitis in the rabbit*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

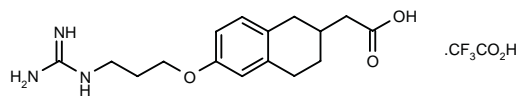
6. Zhan, G. et al. *A prostaglandin DP receptor agonist increases uveoscleral outflow in normotensive monkey eyes*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

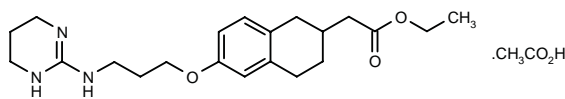
300628

2-[6-(3-Guanidinopropoxy)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid trifluoroacetate



C16 H23 N3 O3 . C2 H F3 O2; Mol wt: 419.3976

ACTION – Agent for the treatment of bone resorption disorders, a selective vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist (IC_{50} = 2.9 μ M) proven active in the osteopontin- $\alpha_v\beta_3$ cell attachment assay (IC_{50} = 8.9 μ M) and the osteoclast pitting assay for bone resorption inhibition (30% inhibition at 238 μ M). Selectivity for vitronectin over $\alpha_{IIb}\beta_3$ was demonstrated by an IC_{50} value of 82.4 μ M for inhibition of ADP-induced human platelet aggregation ($\alpha_{IIb}\beta_3$ -mediated). Compound was also effective in a model of parathyroid hormone (PTH)-induced hypercalcemia in thyroparathyroidectomized male rats following s.c. administration at 100 mg/kg. Another compound from this series of tetrahydro- and dihydroquinoline, tetrahydronaphthalene and tetrahydro-5H-benzocycloheptene bicyclic derivatives is:



300630: C21 H31 N3 O3 . C2 H4 O2

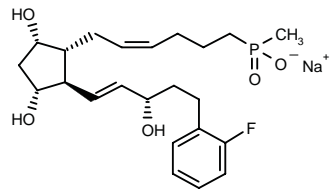
SOURCE – American Home Products.

REFERENCES

1. Zask, A. et al. (American Home Products Corp.) *Bicyclic antagonists selective for the $\alpha_v\beta_3$ integrin*. WO 0107036.

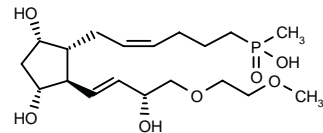
301112

6-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*,3*S*)-5-(2-Fluorophenyl)-3-hydroxy-1-pentenyl]-3,5-dihydroxycyclopentyl]-4(*Z*)-hexenyl(methyl)phosphinic acid sodium salt



C23 H33 F Na O5 P; Mol wt: 462.4707

ACTION – Prostaglandin F analogue that is potentially useful for the treatment of bone disorders and glaucoma. It is reported to increase trabecular number, bone volume and mass while maintaining normal bone turnover rate, and to increase bone formation at the endosteal surface without increasing cortical porosity. Another exemplified compound is:



301113: C19 H35 O7 P

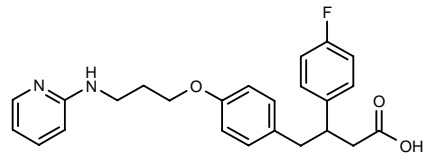
SOURCE – Procter & Gamble.

REFERENCES

1. Delong, M.A. et al. (The Procter & Gamble Co.) *Novel 2-decarboxy-2-phosphinico prostaglandin F analogs*. WO 0110873.

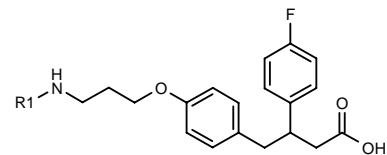
301676

3-(4-Fluorophenyl)-4-[4-[3-(pyridin-2-ylamino)propoxy]-phenyl]butyric acid



C24 H25 F N2 O3; Mol wt: 408.4705

ACTION – Integrin, particularly $\alpha_v\beta_3$ (vitronectin receptor), antagonist useful for the treatment or prevention of angiogenesis, thrombosis, cardiovascular disorders, atherosclerosis, cancer, osteoporosis, inflammation, infections and wound healing. Other specifically claimed compounds are:



Compound	R1	Formula
301677	6-NH2-2-Pyr	C ₂₄ H ₂₆ FN ₃ O ₃
301678	2-NH2-5-imidazolyl	C ₂₂ H ₂₅ FN ₄ O ₃

4. Hellberg, M.R. et al. *The clinical efficacy of AL-6598, DP prostaglandin analog, alone and in combination with brimonidine*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

5. Varnell, E.D. et al. *Effect of AL0-6598, a D-series prostaglandin, on severity and recurrences of herpetic keratitis in the rabbit*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

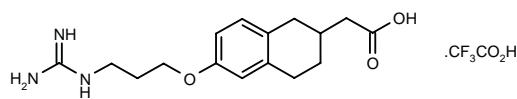
6. Zhan, G. et al. *A prostaglandin DP receptor agonist increases uveoscleral outflow in normotensive monkey eyes*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

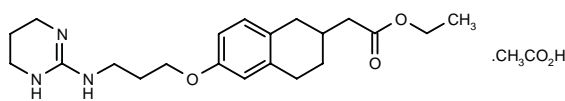
300628

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300630: C21 H31 N3 O3 . C2 H4 O2

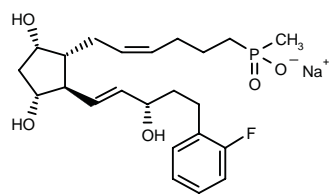
SOURCE – American Home Products.

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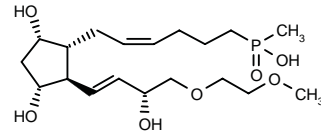
301112

6-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*,3*S*)-5-(2-Fluorophenyl)-3-hydroxy-1-pentenyl]-3,5-dihydroxycyclopentyl]-4(*Z*)-hexenyl(methyl)phosphinic acid sodium salt



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301113: C19 H35 O7 P

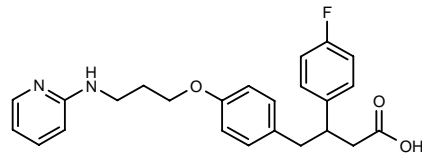
SOURCE – Procter & Gamble.

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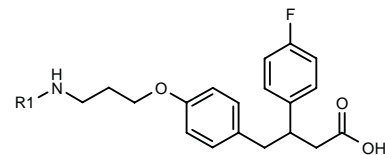
301676

3-(4-Fluorophenyl)-4-[4-[3-(pyridin-2-ylamino)propoxy]-phenyl]butyric acid



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ACTION – Integrin, particularly $\alpha_v\beta_3$ (vitronectin receptor), antagonist useful for the treatment or prevention of angiogenesis, thrombosis, cardiovascular disorders, atherosclerosis, cancer, osteoporosis, inflammation, infections and wound healing. Other specifically claimed compounds are:



Compound	R1	Formula
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301678	2-NH2-5-imidazolyl	C ₂₂ H ₂₅ FN ₄ O ₃

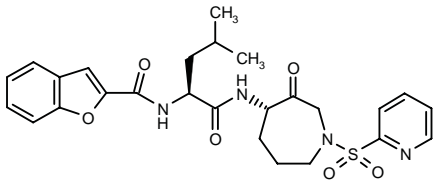
SOURCE – Merck KGaA.

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1. Jonczyk, A. et al. (Merck Patent GmbH) *Novel integrin $\alpha_v\beta_3$ inhibitors*. DE 19939981, WO 0114338.

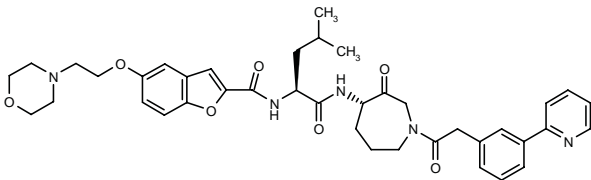
302658

N-[3-Methyl-1 (*S*)-[*N*-[3-oxo-1-(pyridin-2-ylsulfonyl)-perhydroazepin-4(*S*)-yl]carbamoyl]butyl]benzofuran-2-carboxamide



C26 H30 N4 O6 S; Mol wt: 526.6110

ACTION – Potent, competitive and reversible inhibitor of human cathepsin K (K_i = 0.16 nM), selective over human cathepsin L, cathepsin S and cathepsin B (K_i = 2.2, 4.0 and 500 nM, respectively). In addition, compound strongly inhibited native cathepsin K in an *in vitro* cell-based assay of bone resorption (IC_{50} = 70 nM) and inhibited cathepsin activity in human osteoclasts (IC_{50} = 80 nM). *In vivo*, compound was found to significantly inhibit bone resorption when given at a dose of 12 mg/kg s.c. once daily to ovariectomized monkeys. In pharmacokinetic studies in rats, compound showed good oral availability (42%), with a half-life of 30 min and a clearance of 50 ml/min/kg. Potentially useful for the treatment of osteoporosis. Another protease inhibitor is:



302659: C40 H47 N5 O7

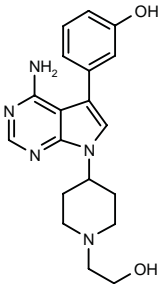
SOURCE – GlaxoSmithKline.

REFERENCES

1. Marquis, R.W. Jr. et al. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 0038687.
2. Marquis, R.W. et al. *Azepanone-based inhibitors of human and rat cathepsin K*. J Med Chem 2001, 44(9): 1380.

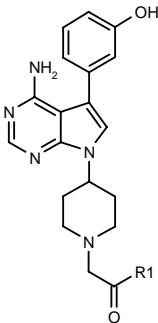
302724

3-[4-Amino-7-[1-(2-hydroxyethyl)piperidin-4-yl]-7 *H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenol



C19 H23 N5 O2; Mol wt: 353.4237

ACTION – Potent and selective inhibitor of c-Src tyrosine kinase (IC_{50} = 1 nM) with remarkable selectivity over epidermal growth factor (EGF) tyrosine kinase and v-Abl tyrosine kinase (IC_{50} = 2.54 and 0.098 μ M, respectively). Compound exhibited good cellular activity, as demonstrated by inhibition of c-Src-mediated phosphorylation of Fak in IC8.1 fibroblasts (IC_{50} = 0.6 μ M). Potentially useful for the treatment of bone diseases. Within this series of 7-heterocyclic-5-aryl-pyrrolo[2,3-*d*]pyrimidines, the following are also described:



Compound	R1	Formula
302721	OMe	C ₂₀ H ₂₃ N ₅ O ₃
302722	NH2	C ₁₉ H ₂₂ N ₆ O ₂
302723	N(Me)2	C ₂₁ H ₂₆ N ₆ O ₂

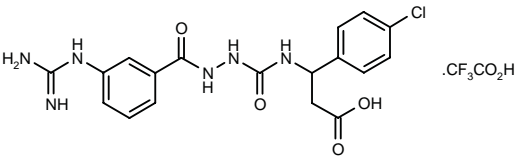
SOURCE – Novartis.

REFERENCES

1. Altmann, E. et al. *7-Pyrrolidinyl- and 7-piperidinyl-5-aryl-pyrrolo[2,3-d]pyrimidines-potent inhibitors of the tyrosine kinase c-Src*. Bioorg Med Chem Lett 2001, 11(6): 853.

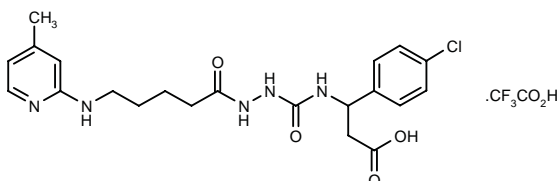
303686

3-(4-Chlorophenyl)-3-[3-(3-guanidinobenzoyl)carbazoylamino]propionic acid trifluoroacetate



C18 H19 Cl N6 O4 . C2 H F3 O2; Mol wt: 532.8610

ACTION – Potent nonpeptide integrin $\alpha_v\beta_3$ antagonist ($IC_{50} = 0.1$ nM) with > 10,000-fold selectivity over integrin $\alpha_{IIb}\beta_3$ receptors and promising properties for oral bioavailability. Potentially useful for the treatment of $\alpha_v\beta_3$ receptor-related pathologies including osteoporosis, restenosis following coronary angioplasty, acute renal failure, ocular diseases, tumor-induced angiogenesis and metastasis formation. Another diacylhydrazine derivative is:



303687: C₂₁ H₂₆ Cl N₅ O₄ . C₂ H F₃ O₂

SOURCE – Merck KGaA.

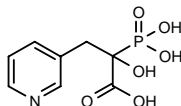
REFERENCES

1. Holzemann, G. et al. (Merck Patent GmbH) *Diacylhydrazine derivs.* DE 19932796, WO 0105753.
2. Sulyok, G.A.G. et al. *Solid-phase synthesis of a nonpeptide RGD mimetic library: New selective $\alpha_v\beta_3$ integrin antagonists.* J Med Chem 2001, 44(12): 1938.

NE-10790

304483

2-Hydroxy-2-phosphono-3-(3-pyridyl)propionic acid



C₈ H₁₀ N O₆ P; Mol wt: 247.1420

ACTION – Phosphonocarboxylate analogue of risedronate with less activity than the parent compound against J774 macrophage viability and bone resorption by rabbit osteoclasts. Compound, unlike risedronate, was found to selectively inhibit geranylgeranyltransferase II (IC_{50} approx. 600 μ M) and was a very weak inhibitor of FPP synthase. Potentially useful for the treatment of bone diseases such as osteoporosis.

SOURCE – Procter & Gamble.

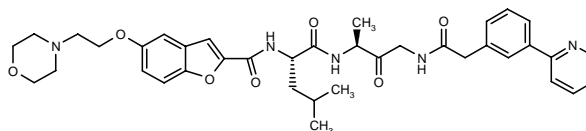
REFERENCES

1. Ebetino, F.H. et al. (The Procter & Gamble Co.) *Phosphonocarboxylate cpds. for treating abnormal calcium and phosphate metabolism.* EP 0788362, EP 0849272, US 5391743, US 5824661, WO 9324131.
2. Boissier, S. et al. *Biphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases.* Cancer Res 2000, 60(11): 2949.
3. Coxon, F.P. et al. *Identification of a phosphonocarboxylate analogue of risedronate which inhibits geranylgeranyl transferase II and selectively prevents prenylation of Rab proteins in osteoclasts.* Bone 2001, 28(5, Suppl.): Abst SC2 W.
4. van Beek, E.R. et al. *Binding and antiresorptive properties of heterocycle-containing bisphosphonate analogs: Structure-activity relationships.* Bone 1998, 23(5): 437.

SB-290190

303607

N-[*N*-[5-[2-(4-Morpholinyl)ethoxy]-1-benzofuran-2-yl-carbonyl]-L-leucyl-L-alanylmethyl]-2-[3-(2-pyridyl)phenyl]-acetamide



C₃₈ H₄₅ N₅ O₇; Mol wt: 683.8015

ACTION – Human cathepsin K inhibitor ($K_i = 0.05$ nM) with about 72-fold selectivity over cathepsin L ($K_i = 3.58$ nM), proven to strongly inhibit osteoclast cathepsin activity in a cytochemical assay ($IC_{50} = 63$ nM). Compound was found to inhibit *in vitro* human osteoclast-mediated bone resorption ($IC_{50} = 71$ nM). Potentially useful for the treatment of osteoporosis.

SOURCE – GlaxoSmithKline.

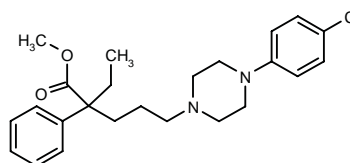
REFERENCES

1. Bondinell, W.E. et al. (SmithKline Beecham Corp.) *Protease inhibitors.* WO 9959526.
2. James, I.E. et al. *Potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro.* J Biol Chem 2001, 276(15): 11507.

TREATMENT OF LIPOPROTEIN DISORDERS

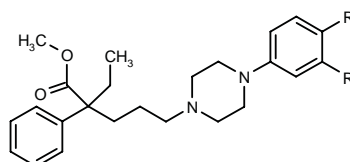
301683

5-[4-(4-Chlorophenyl)piperazin-1-yl]-2-ethyl-2-phenyl-pentanoic acid methyl ester



C₂₄ H₃₁ Cl N₂ O₂; Mol wt: 414.9739

ACTION – Microsomal triglyceride transfer protein (MTP) inhibitor with potential for the treatment of hyperlipidemia, atherosclerosis, obesity, diabetes mellitus and pancreatitis. Other specifically claimed compounds from this series of substituted piperazine derivatives are:



Compound	R1	R2	Formula
301684	Ph	H	C ₃₀ H ₃₆ N ₂ O ₂
301685	H	Ph	C ₃₀ H ₃₆ N ₂ O ₂

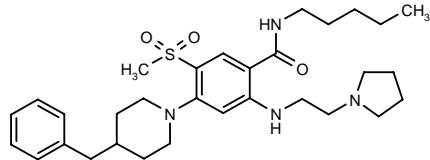
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Lehmann-Lintz, T. et al. (Boehringer Ingelheim Pharma KG) *Substd. piperazine derivs., the production thereof and their utilization as medicaments*. DE 19939516, DE 19939745, WO 0114355.

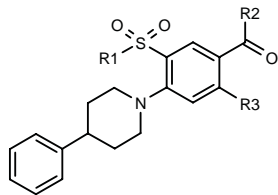
301923

4-(4-Benzylpiperidin-1-yl)-5-(methylsulfonyl)-*N*-pentyl-2-[2-(1-pyrrolidinyl)ethylamino]benzamide



C31 H46 N4 O3 S; Mol wt: 554.7954

ACTION – Hypolipidemic agent proven to stimulate the expression of LDL receptor in a luciferase reporter gene assay using HepG2 cells transfected with a human LDL receptor gene expression vector (221% at 0.15 μM and 197% at 0.05 μM [controls = 100%]). *In vivo*, compound decreased total cholesterol, LDL cholesterol and tryglyceride levels by 16, 57 and 11% in cholesterol-fed hamsters at 20 mg/kg/day p.o. x 10 days. Other compounds from this series of sulfonyl carboxamide derivatives include the following:



Compound	R1	R2	R3	Formula
301924	1-Pip	1-Pip	4-Me-1-Piz	C ₃₃ H ₄₇ N ₅ O ₃ S
301925	CH2Ph	N(Et)2	N(Et)CH2CH2N(Me)2	C ₃₈ H ₄₈ N ₄ O ₃ S

SOURCE – Aventis Pharma.

REFERENCES

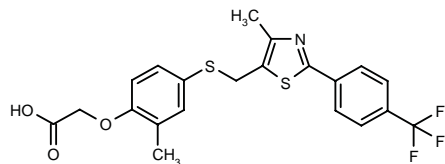
1. Kirsch, R. et al. (Aventis Pharma Deutschland GmbH) *Sulfonyl carboxamide derivs., method for their production and their use as medicaments*. DE 19941540, WO 0116094.

GW-501516

299373

2-[2-Methyl-4-[4-methyl-2-[4-(trifluoromethyl)phenyl]-thiazol-5-ylmethylsulfonyl]phenoxy]acetic acid

GW-516



C21 H18 F3 N O3 S2; Mol wt: 453.5032

ACTION – Selective agonist of peroxisome proliferator-activated receptor PPARδ with high affinity for the human receptor in a binding assay (K_i = 1.1 nM) and potent and selective agonist activity in a cell-based transfection assay (EC₅₀ = 1.2 nM and > 1,000-fold selectivity relative to other PPAR subtypes). Compound increased mRNA expression of the reverse cholesterol transporter ATP-binding cassette A1 in macrophages, human fibroblasts and intestinal cells, and induced apolipoprotein A-I-specific cholesterol efflux. In a model of human metabolic syndrome X using insulin-resistant middle-aged obese rhesus monkeys, compound given at a dose of 3.0 mg/kg p.o. b.i.d. produced marked effects on the serum lipid profile. It significantly increased HDL cholesterol (79%) and decreased fasting triglycerides (56%), VLDL cholesterol (50%) and LDL cholesterol levels (29%); it also significantly reduced serum insulin levels (48%) without adverse effects on glycemic control. Potentially useful for reducing the incidence of cardiovascular disease associated with metabolic syndrome X. Compound is undergoing phase I clinical studies.

SOURCES – GlaxoSmithKline; Ligand.

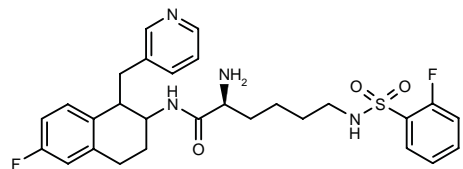
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1. Chao, E.Y.-H. et al. (Glaxo Group Ltd.) *Thiazole and oxazole derivs. and their pharmaceutical use*. WO 0100603.
2. Oliver, W.R. Jr. et al. *A selective peroxisome proliferator-activated receptor δ agonist promotes reverse cholesterol transport*. Proc Natl Acad Sci USA 2001, 98(9): 5306.
3. *Atherosclerosis*. Drug R&D Backgrounders.
4. *GlaxoSmithKline updates R&D activities —Merger makes way for robust pipeline*. DailyDrugNews.com (Daily Essentials) 2001, March 1.
5. *Ligand Pharmaceuticals. An emerging specialty pharmaceutical company*. Ligand Pharmaceuticals Web Site 2001, April 30.
6. *Product development pipeline*. GlaxoSmithKline Product Pipeline 2001 February.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

301033

*N*⁶-(2-Fluorophenylsulfonyl)-*N*¹-[6-fluoro-1-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-L-lysineamide



C28 H32 F2 N4 O3 S; Mol wt: 542.6478

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist (93% inhibition of [¹²⁵I]-PYY binding to the human NPY Y₅ receptor cloned in HEK293 cells at 300 nM) proven to reduce food intake in fasted rats at 30 mg/kg i.p. (85.3, 75.4 and 73.1% reduction at 2, 4 and 6 h post-administration, respectively). Potentially useful for the treatment of NPY Y₅-mediated disorders such as obesity, anorexia nervosa, bulimia nervosa, depression, anxiety, diabetes, memory loss, epileptic seizures, migraine, sleep disturbances, pain and sexual/reproductive disorders. A representative compound from a series of amine and amide derivatives.

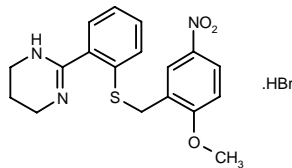
SOURCE – Ortho-McNeil.

REFERENCES

1. Dax, S.L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Amine and amide derivs. as ligands for the neuropeptide Y Y5 receptor useful in the treatment of obesity and other disorders.* WO 0109120.

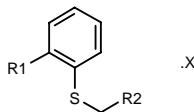
301128

2-[2-(2-Methoxy-5-nitrobenzylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine hydrobromide



C18 H19 N3 O3 S . HBr; Mol wt: 438.3440

ACTION – Agent for the treatment of MC₄ receptor-associated disorders, particularly weight loss due to cachexia or anorexia and pigmentation disorders, with very potent inhibition of MC₄ in a scintillation proximity assay (SPA) and at least 100-fold selectivity for MC₄ over MC₁, MC₃ and MC₅ in a cAMP assay in transfected HEK293 cells. In addition, it exhibited MC₄ receptor-antagonist activity *in vivo*, partially reversing the effects of the administration of MC₄ agonist MTII in food-deprived mice following i.c.v. injection of 15 nmol prior to MTII injection. Other compounds from this series of MC₄ receptor-binding compounds include the following:



Compound	R1	R2	X	Formula
301131	3,4,5,6-tetrahydro-2-pyrimidinyl	1-Naph	HCl	C ₂₁ H ₂₀ N ₂ S.HCl
301139	3a,4,5,6,7,7a-hexahydro-2-benzimidazolyl	2-MeO-5-NO ₂ -Ph	HBr	C ₂₁ H ₂₃ N ₃ O ₃ S.HBr
301140	3,4,5,6-tetrahydro-2-pyrimidinyl	2-MeO-1-Naph	HCl	C ₂₂ H ₂₂ N ₂ OS.HCl
301141	3,4,5,6-tetrahydro-2-pyrimidinyl	5-Br-2-MeO-Ph	HCl	C ₁₈ H ₁₉ BrN ₂ OS.HCl

SOURCE – Millennium.

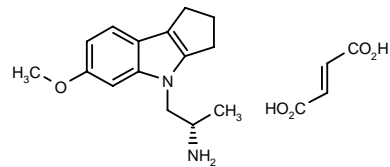
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1. Maguire, M.P. et al. (Millennium Pharmaceuticals, Inc.) *Melanocortin-4 receptor binding cpds. and methods of use thereof.* WO 0110842.

301332

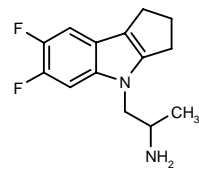
1-(6-Methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indol-4-yl)propan-2(*S*)-amine fumarate

2-(6-Methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indol-4-yl)-1(*S*)-methylethylamine fumarate



C15 H20 N2 O . C4 H4 O4; Mol wt: 360.4076

ACTION – Antiobesity agent, a selective 5-HT_{2C} agonist with K_i values of 63, 314 and 210 nM for 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptors, respectively, in binding assays. Its functional activity was determined in CHO cells expressing human 5-HT_{2C} and 5-HT_{2A} receptors, exhibiting respective EC₅₀ values of 1686 and 89 nM. Another exemplified indole derivative is:



301333: C14 H16 F2 N2

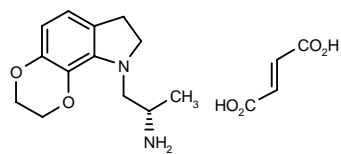
SOURCE – Vernalis.

REFERENCES

1. Bentley, J.M. et al. (Vernalis Research Ltd.) *Indole derivs., process for their preparation, pharmaceutical compsns. containing them and their medicinal application.* WO 0112603.

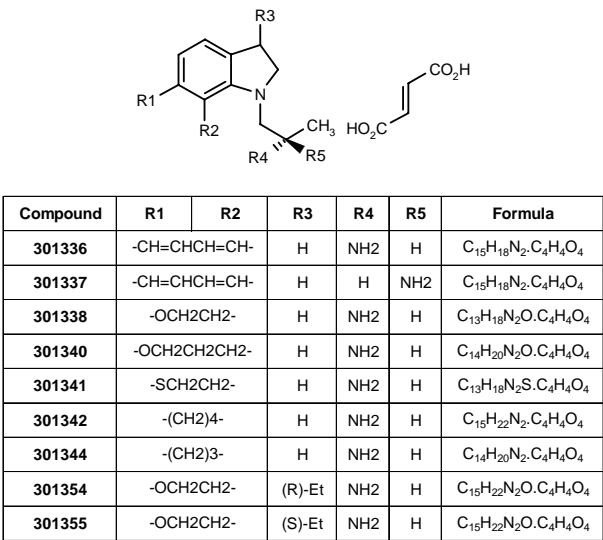
301334

1-(3,7,8,9-Tetrahydro-2*H*-[1,4]dioxino[2,3-*g*]indol-9-yl)-propan-2(*S*)-amine fumarate



C13 H18 N2 O2 . C4 H4 O4; Mol wt: 350.3688

ACTION – Antiobesity agent, a selective 5-HT_{2C} agonist with K_i values of 70, 218 and 223 nM for 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptors, respectively, in binding assays. Its functional activity was determined in CHO cells expressing human 5-HT_{2C} and 5-HT_{2A} receptors, exhibiting respective EC₅₀ values of 48 and 0.4 nM. Other exemplified indole derivatives include the following:



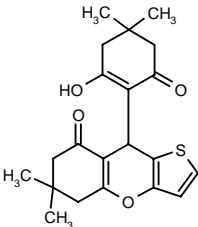
SOURCE – Vernalis.

REFERENCES

1. Roffey, J.R.A. et al. (Vernalis Research Ltd.) *Condensed indoline derivs. and their use as 5HT_{2C} receptor ligands*. WO 0112602.

301484

9-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-6,6-dimethyl-6,7,8,9-tetrahydro-5H-thieno[3,2-*b*]-1-benzopyran-8-one



C21 H24 O4 S; Mol wt: 372.4826

ACTION – Agent with affinity for neuropeptide Y (NPY) Y₅ receptor (90% inhibition of [³H]-NPY binding to human Y₅ receptors at 10 μM), also reported to decrease NPY-induced eating in rats. Potentially useful for the treatment of eating or metabolic disorders such as obesity, anorexia, diabetes, arteriosclerosis and hypercholesterolemia, as well as for the treatment of CNS disorders such as depression, epilepsy and dementia. A representative compound from a series of thiophene derivatives.

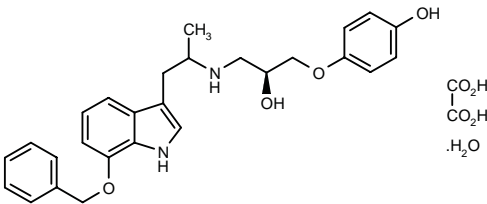
SOURCE – Meiji Seika.

REFERENCES

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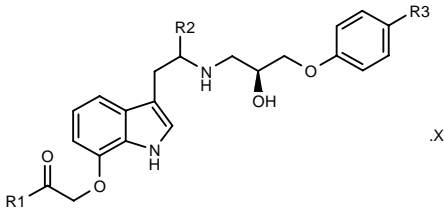
301487

4-[3-[2-[7-(Benzyloxy)-1*H*-indol-3-yl]-1-methylethylamino]-2(*S*)-hydroxypropoxy]phenol oxalate hydrate



C27 H30 N2 O4 . C2 H2 O4 . H2O; Mol wt: 554.5926

ACTION – Antiobesity and antidiabetic agent, a potent and selective β₃-adrenoceptor agonist (EC₅₀ = 0.22 nM for increasing cAMP levels in CHO cells expressing the human receptor). Within this series of 3,7-disubstituted indole derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
301489	N(Et)2	(R)-Me	OH	oxalate .H2O	C ₂₆ H ₃₅ N ₃ O ₅ .C ₂ H ₂ O ₄ .H ₂ O
301490	OH	(R)-Me	OH	4H2O	C ₂₂ H ₂₆ N ₂ O ₆ .4H ₂ O
301491	OH	Me	H		C ₂₂ H ₂₆ N ₂ O ₅

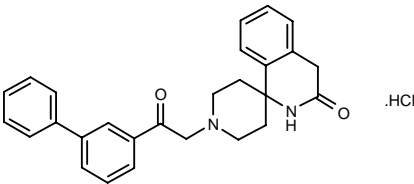
SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Kato, S. et al. (Dainippon Pharmaceutical Co., Ltd.) *3,7-Disubstd. indole derivs. and medicinal compsns. containing them*. JP 2001039948.

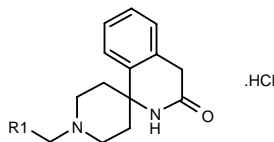
301703

1'-[2-(3-Biphenyl)-2-oxoethyl]-1,2,3,4-tetrahydrospiro-[isoquinoline-1,4'-piperidin]-3-one hydrochloride



C27 H26 N2 O2 . HCl; Mol wt: 446.9753

ACTION – Selective neuropeptide Y (NPY) Y₅ receptor antagonist for promoting weight loss and for the treatment of eating disorders. A representative compound from a series of spiroisquinolinone derivatives, wherein the following are also included:



Compound	R1	Formula
301704	4-Ph-PhCOCH2	C ₂₈ H ₂₈ N ₂ O ₂ .HCl
301705	4-Ph-PhCOCH2CH2	C ₂₉ H ₃₀ N ₂ O ₂ .HCl
301706	4-Ph-Ph-CH(OH)	C ₂₇ H ₂₈ N ₂ O ₂ .HCl

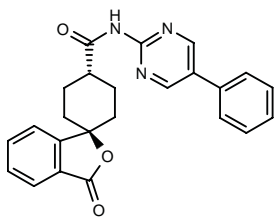
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Poindexter, G.S. et al. (Bristol-Myers Squibb Co.) *NPY antagonists: Spiro-isoquinolinone derivs.* WO 0113917.

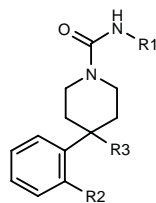
301796

trans-3'-Oxo-*N*-(5-phenylpyrimidin-2-yl)spiro[cyclohexane-1,1'(3'*H*)-isobenzofuran]-4-carboxamide

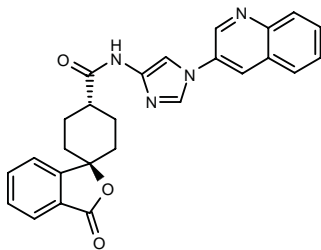


C₂₄ H₂₁ N₃ O₃; Mol wt: 399.4479

ACTION – Agent for the treatment of eating or metabolic disorders such as obesity, bulimia and diabetes, a neuropeptide Y (NPY) Y₅ receptor antagonist (IC₅₀ = 0.48 nM against [¹²⁵I]-PYY binding to human Y₅ receptors). Other exemplified compounds from this series of spiro compounds include the following:



Compound	R1	R2,R3	Formula
301798	4-(PhCO)-Ph	-CONH-	C ₂₆ H ₂₃ N ₃ O ₃
301799	1-(2-quinolyl)-4-imidazolyl	-CH2CONH-	C ₂₆ H ₂₄ N ₆ O ₂
301801	5-Ph-2-pyrazinyl	-COO-	C ₂₃ H ₂₀ N ₄ O ₃
301802	7-CF3-1,5-naphthyridin-2-yl	-COO-	C ₂₂ H ₁₇ F ₃ N ₄ O ₃
301803	5-(3-F-Ph)-2-pyrimidinyl	-COO-	C ₂₃ H ₁₉ FN ₄ O ₃
301805	4-(PhCO)-Ph	-CH2COO-	C ₂₇ H ₂₄ N ₂ O ₄



301806: C₂₆ H₂₂ N₄ O₃

SOURCE – Banyu.

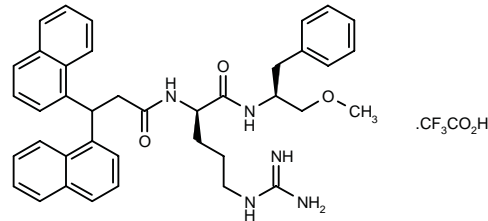
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GI-264879A

303590

*N*¹-[1 (*S*)-Benzyl-2-methoxyethyl]-*N*²-[3,3-di(1-naphthyl)-propionyl]-*D*-argininamide trifluoroacetate



C₃₉ H₄₃ N₅ O₃ . C₂ H F₃ O₂; Mol wt: 743.8226

ACTION – Nonselective neuropeptide Y (NPY) Y₁ receptor antagonist that produced long-lasting and dose-dependent inhibition of NPY-induced food intake in rats. Compound showed affinities ranging between 1 μM and 18 μM for cloned human NPY receptors (Y₁>Y₄>Y₅>Y₂), as well as for rat hypothalamic NPY receptors (IC₅₀ = 1.5 μM) and functional antagonism for Y₁ receptors in human erythroleukemia cells. In satiated rats, compound given i.p. at a dose of 10 mg/kg significantly reduced food intake induced by NPY or NPY (2-36). In schedule-fed and 20-h food-deprived rats, a single dose of compound (1-10 mg/kg i.p.) produced a long-lasting and dose-dependent inhibition of food intake. In genetically obese Zucker rats, compound given once daily for 21 days at 2.5 mg/kg/day i.p. resulted in an initial weight loss, followed by weight gain at a significantly lower rate than control animals. In this experiment, it was found to induce a significant reduction in plasma triglycerides throughout the treatment period, as well as in body fat mass. The reduction in food intake and body weight is mediated by both a direct interaction with NPY receptors and through a vagus nerve-mediated mechanism. Potentially useful as an antiobesity agent.

SOURCE – GlaxoSmithKline.

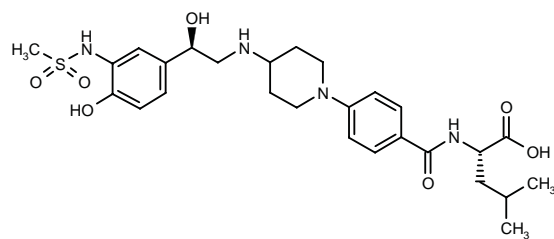
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WAY-174231

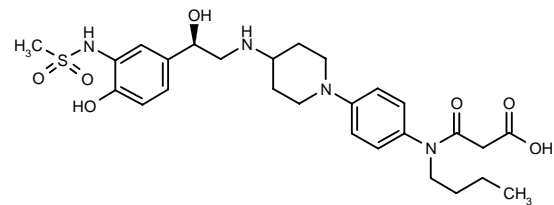
302705

N-[4-[4-[2(R)-Hydroxy-2-[4-hydroxy-3-(methylsulfonylamido)phenyl]ethylamino]piperidin-1-yl]benzoyl]-L-leucine



C27 H38 N4 O7 S; Mol wt: 562.6842

ACTION – Potent and selective human β_3 -adrenoceptor agonist with an EC_{50} 8 nM and 96% intrinsic activity (IA) in CHO cells expressing human β_3 -adrenoceptors and only 6% and 8% IA in CHO cells expressing β_1 - and β_2 -adrenoceptors, respectively. *In vivo*, compound showed a good thermogenic effect in human β_3 -adrenoceptor transgenic mice (51% thermogenesis at 10 mg/kg i.p.). Potentially useful for the treatment of obesity. Another related compound is:



302706: C27 H38 N4 O7 S

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Hu, B. et al. (4-Piperidin-1-yl)phenyl amides: Potent and selective human β_3 agonists. J Med Chem 2001, 44(9): 1456.

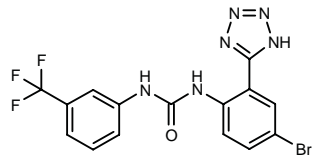
2. Sum, F.-W. et al. Cyclylamines as conformationally restricted linkers in the design and synthesis of novel β_3 adrenergic receptor agonists. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 345.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

NS-3623

303026

N-[4-Bromo-2-(1H-tetrazol-5-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea



C15 H10 Br F3 N6 O; Mol wt: 427.1830

ACTION – Potent and reversible chloride (Cl^-) conductance blocker potentially useful for the treatment of sickle cell disease. The compound reversibly blocked Cl^- conductance *in vitro* in red blood cells (RBCs) from both normal human and sickle cell patients (IC_{50} = 210 nM), and *in vivo* in murine RBCs following both i.v. and p.o. (ED_{50} = 25 mg/kg) administration, with significant activity sustained for up to 5 h following oral doses of 100 mg/kg or more. No toxicity was observed in mice and rats treated orally at doses of up to 100 mg/kg b.i.d. for 9 days. In a transgenic mouse model of sickle cell disease, compound given at oral doses of 10-100 mg/kg b.i.d. for 3 weeks dose-dependently increased total intracellular cations and hematocrit, and decreased mean cellular hemoglobin concentration. Moreover, compound produced a change in erythrocyte morphology from predominantly sickled forms to a high proportion of well-hydrated nonsickled forms. All these changes were reversible by 1 month after withdrawal of compound.

SOURCE – NeuroSearch.

REFERENCES

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3. Bennekou, P. et al. Specific blockers of chloride conductance, NS1652 and NS3623, reduce sickle cell dehydration *in vitro* and *in vivo*. Blood 1999, 94(10, Suppl. 1): 677a.

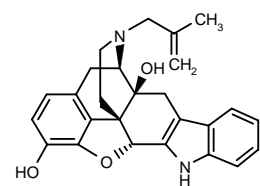
4. Bennekou, P. et al. Treatment with NS3623, a novel Cl^- conductance blocker, ameliorates erythrocyte dehydration in transgenic SAD mice: A possible new therapeutic approach for sickle cell disease. Blood 2001, 97(5): 1451.

TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

302708

17-(2-Methyl-2-propenyl)-4,5 α -epoxy-3,14-dihydroxy-6,7-didehydroindolo[2',3':6,7]morphinan

(4bS,8R,8aS,14bR)-7-(2-Methyl-2-propenyl)-6,7,8,9,14,14b-hexahydro-5H-4,8-methano[1]benzofuro[2,3-a]pyrido[4,3-b]carbazole-1,8a-diol

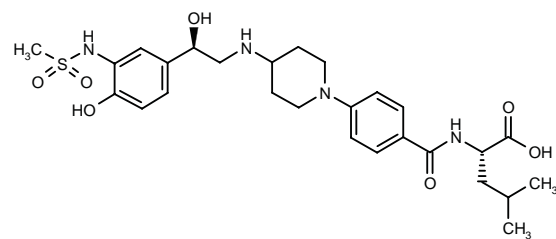


C26 H26 N2 O3; Mol wt: 414.5024

WAY-174231

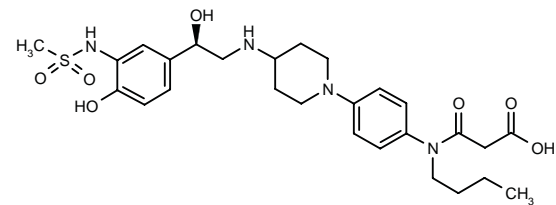
302705

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302706: C27 H38 N4 O7 S

SOURCE – Wyeth-Ayerst.

REFERENCES

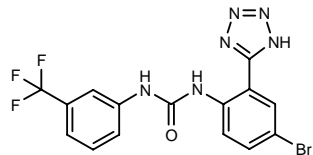
1. Hu, B. et al. (4-Piperidin-1-yl)phenyl amides: Potent and selective human β_3 agonists. J Med Chem 2001, 44(9): 1456.
2. Sum, F.-W. et al. Cyclylamines as conformationally restricted linkers in the design and synthesis of novel β_3 adrenergic receptor agonists. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MED1 345.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

NS-3623

303026

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SOURCE – NeuroSearch.

REFERENCES

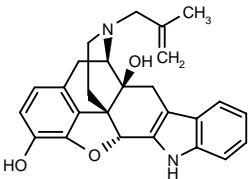
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3. Bennekou, P. et al. Specific blockers of chloride conductance, NS1652 and NS3623, reduce sickle cell dehydration *in vitro* and *in vivo*. Blood 1999, 94(10, Suppl. 1): 677a.
4. Bennekou, P. et al. Treatment with NS3623, a novel Cl^- conductance blocker, ameliorates erythrocyte dehydration in transgenic SAD mice: A possible new therapeutic approach for sickle cell disease. Blood 2001, 97(5): 1451.

TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

302708

17-(2-Methyl-2-propenyl)-4,5 α -epoxy-3,14-dihydroxy-6,7-didehydroindolo[2',3':6,7]morphinan

(4bS,8R,8aS,14bR)-7-(2-Methyl-2-propenyl)-6,7,8,9,14,14b-hexahydro-5H-4,8-methano[1]benzofuro[2,3-a]pyrido[4,3-b]carbazole-1,8a-diol



C26 H26 N2 O3; Mol wt: 414.5024

ACTION – Delta opioid receptor antagonist with high affinity and selectivity for delta over mu and kappa opioid receptors ($K_i = 4.7, 7900$ and 3800 nM, respectively). Compound showed *in vitro* functional antagonist activity in the [35 S]GTP γ binding assay ($K_i = 1.2, 200$ and 740 nM for inhibition of agonist-stimulated [35 S]GTP γ binding at delta, mu and kappa receptors, respectively), as well as in mouse vas deferens ($K_e = 8.9$ nM), but not in guinea pig ileum longitudinal muscle myenteric plexus ($K_e > 20$ μ M). Compound was much more selective than naltrindole in both binding and functional assays. Potentially useful for the treatment of cocaine abuse.

SOURCES – University of Arizona, Tucson, AZ (US); National Institute on Drug Abuse, Bethesda, MD (US); National Institutes of Health, Bethesda, MD (US).

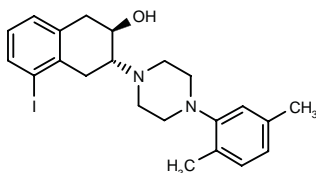
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1. McLamore, S. et al. *Effect of N-alkyl and N-alkenyl substituents in noroxymorphindole, 17-substituted-6,7-dehydro-4,5 α -epoxy-3,14-dihydroxy-6,7:2',3'-indolomorphinans on opioid receptor affinity, selectivity, and efficacy.* J Med Chem 2001, 44(9): 1471.

DIAGNOSTIC AGENTS

300820

(-)-*trans*-3-[4-(2,5-Dimethylphenyl)piperazin-1-yl]-5-iodo-1,2,3,4-tetrahydronaphthalen-2-ol



C22 H27 I N2 O; Mol wt: 462.3683

ACTION – Agent with potent and selective affinity for vesamicol receptors, as demonstrated in binding assays by IC_{50} values of 0.58, 61.2, 1500, 240 and $> 20,000$ nM, respectively, for vesamicol receptors, α_1 -adrenoceptors, σ_1 receptors, 5-HT $_{1A}$ and 5-HT $_{2A}$ receptors. Compound was shown to distribute in choline nerve-rich areas of the brain such as the striatum and is reported to be useful for the diagnosis of brain disorders, particularly Alzheimer's disease. A representative compound from a series of vesamicol piperazine derivatives.

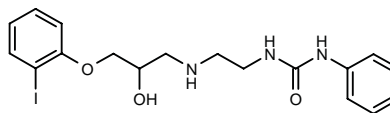
SOURCE – Daiichi Radioisotope.

REFERENCES

1. Bando, K. et al. (Daiichi Radioisotope Labs., Ltd.) *Vesamicol piperazine derivs. and drugs containing the same.* WO 0107427.

303694

N-[2-[2-Hydroxy-3-(2-iodophenoxy)propylamino]ethyl]-*N'*-phenylurea



C18 H22 I N3 O3; Mol wt: 455.2898

ACTION – β_1 -Adrenoceptor antagonist with subnanomolar affinity and 265-fold selectivity for β_1 - over β_2 -adrenoceptors ($K_i = 0.04$ and 12 nM, respectively). The radioactive forms (125 I or 123 I) may be suitable for pharmacokinetic studies and for selective labeling of β_1 -adrenoceptors in patients using single-photon emission tomography.

SOURCE – Westfälische Wilhelms-Universität, Münster (DE).

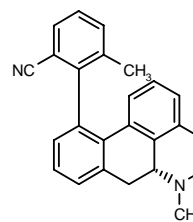
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PHARMACOLOGICAL TOOLS

302654

3-Methyl-2-[(6a*R*,a*S*)-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinolin-11-yl]benzonitrile



C25 H22 N2; Mol wt: 350.4628

ACTION – Potent and selective 5-HT $_7$ receptor antagonist with nanomolar binding affinity at 5-HT $_7$ receptors ($K_i = 3.79$) and 37- and 131-fold selectivity versus 5-HT $_{1A}$ and dopamine D2 receptors, respectively. In a functional assay *in vitro*, compound was seen to antagonize 5-HT-induced stimulation of cAMP production in CHO cells expressing 5-HT $_7$ receptors. Potentially useful as a pharmacological tool to elucidate the role of 5-HT $_7$ receptors.

SOURCES – Acadia; AstraZeneca.

REFERENCES

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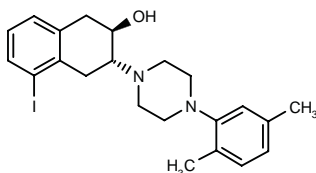
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DIAGNOSTIC AGENTS

300820

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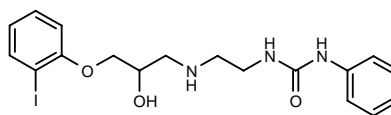
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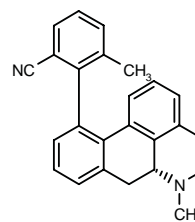
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PHARMACOLOGICAL TOOLS

302654

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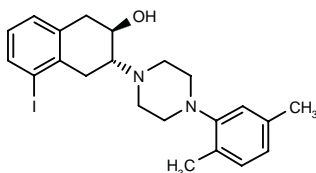
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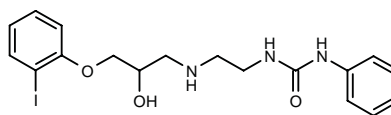
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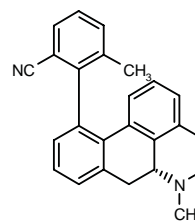
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PHARMACOLOGICAL TOOLS

302654

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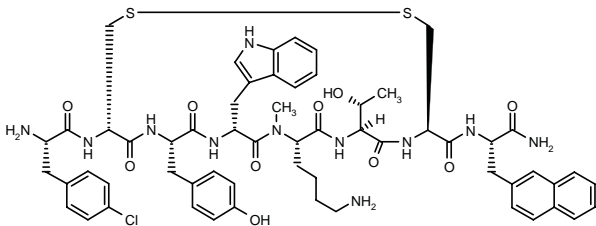
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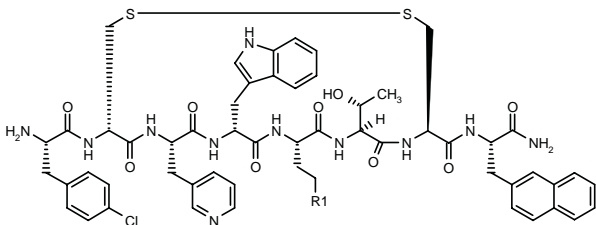
302803

4-Chloro-L-phenylalanyl-D-cysteinyl-L-tyrosyl-D-tryptophyl-N-methyl-L-lysyl-L-threonyl-L-cysteinyl-3-(2-naphthyl)-L-alaninamide cyclic (2-7)-disulfide



C59 H70 Cl N11 O10 S2; Mol wt: 1192.8540

ACTION – Somatostatin sst₂ receptor antagonist with high binding affinity for sst₂ over sst₁, sst₃, sst₄ and sst₅ receptors (K_i = 5.51, 1000, 115.1, 1000 and 70.7 nM, respectively) and *in vitro* functional antagonist activity against somatostatin-induced inhibition of growth hormone release from rat pituitary gland. Potentially useful as a pharmacological tool to elucidate the physiological role of somatostatin sst₂ receptors. Other related compounds are:



Compound	R1	Formula
302802	CH2CH2NH2	C ₅₈ H ₆₉ ClN ₁₂ O ₉ S ₂
303012	NH2	C ₅₆ H ₆₃ ClN ₁₂ O ₉ S ₂

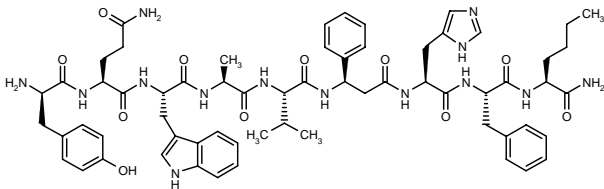
SOURCES – Biomeasure; Tulane University, New Orleans, LA (US).

REFERENCES

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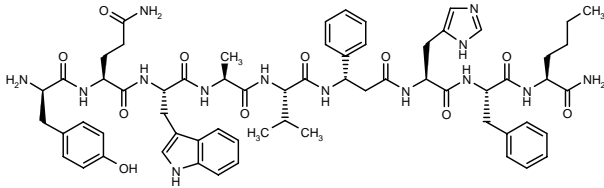
303161

N-[3(R)-(D-Tyrosyl-L-glutaminyL-L-tryptophyl-L-alanyl-L-valylamino)-3-phenylpropionyl]-L-histidyl-L-phenylalanyl-L-norleucinamide



C63 H80 N14 O11; Mol wt: 1209.4120

ACTION – Selective bombesin receptor BRS-3 ligand (K_i = 4.1 nM) with low affinity for the gastrin-releasing receptor (GRP-R, BB2; K_i = 242 nM) and neuromedin B receptor (NMB-R, BB1; K_i = 467 nM). Compound showed *in vitro* functional agonist activity at the BRS-3 receptor, measured as stimulation of the increase in inositol phosphate in BALB cells expressing human BRS-3 receptors. Potentially useful as a pharmacological tool to elucidate the role of BRS-3 receptor activation in obesity, glucose homeostasis, hypertension and other physiological or pathological processes. Another related peptide is:



303162: C63 H80 N14 O11

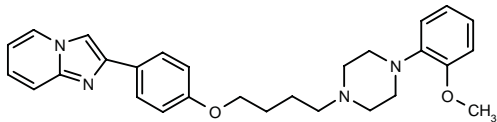
SOURCES – National Institutes of Health, Bethesda, MD (US); Tulane University, New Orleans, LA (US).

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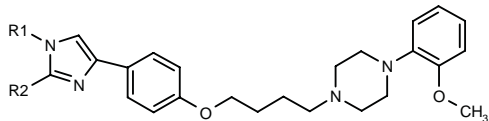
304399

2-[4-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butoxy]-phenyl]imidazo[1,2-a]pyridine



C28 H32 N4 O2; Mol wt: 456.5868

ACTION – Potent and selective dopamine D3 receptor ligand with pK_i values of 9.5, 7.9 and 7.7 for dopamine D3, D2 and histamine 5-HT_{1A} receptors, respectively. Potentially useful as a pharmacological tool to elucidate physiological role of dopamine D3 receptors and their therapeutic potential for the treatment of psychiatric disorders. Other substituted phenoxyalkylpiperazines are:



Compound	R1,R2	Formula
304400	-CH=CHCH=N-	C ₂₇ H ₃₁ N ₅ O ₂
304401	-CH2CH2S-	C ₂₆ H ₃₂ N ₄ O ₂ S

SOURCE – Gedeon Richter.

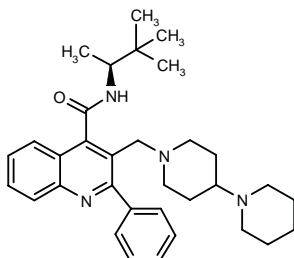
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2. Laszlovszky, I. et al. *Substituted phenoxyalkylpiperazines as dopamine D3 receptor ligands*. Pharmazie 2001, 56(4): 287.

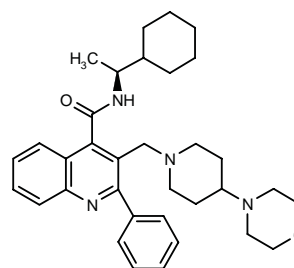
SB-414240^{*,1,3}**290563**

2-Phenyl-3-[4-(1-piperidinyl)piperidin-1-ylmethyl]-*N*-[1(*S*),2,2-trimethylpropyl]quinoline-4-carboxamide



C33 H44 N4 O; Mol wt: 512.7376

ACTION – Potent and selective human NK₂ receptor antagonist ($K_i = 1$ and 193 nM for binding affinity for NK₂ and NK₃ receptors, respectively). Compound showed high affinity over mu opioid receptors ($K_i > 2000$ nM). Suitable as a pharmacological tool for further characterization of the pathophysiological role of NK₂ receptors. Another related compound from this series of quinoline-4-carboxamides is:



SB-400238 [301437]^{2,3}: C34 H44 N4 O2

SOURCE – GlaxoSmithKline.

REFERENCES

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2. Farina, C. et al. (SmithKline Beecham SpA) *Quinoline-4-carboxamide derivs. as NK-3 and NK-2 receptor antagonists*. WO 0031037.
3. Blaney, F.E. et al. *Stepwise modulation of neurokinin-3 and neurokinin-2 receptor affinity and selectivity in quinoline tachykinin receptor antagonists*. J Med Chem 2001, 44(11): 1675.

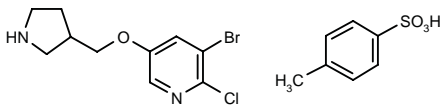
*Identified compound **290563** (see **290562**) Drug Data Rep 2000, 022(10): 0882.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

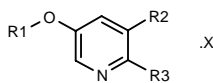
302661

3-Bromo-2-chloro-5-(pyrrolidin-3-ylmethoxy)pyridine
tosylate



C10 H12 Br Cl N2 O . C7 H8 O3 S; Mol wt: 463.7780

ACTION – Agent with potent and selective affinity for neuronal nicotinic acetylcholine receptors ($K_i = 0.042$ nM against [3 H]-cytisine binding in crude synaptic membrane preparations from whole rat brain), proven to exhibit analgesic activity in the mouse hot-plate paradigm (minimum effective dose [MED] = $6.2 \mu\text{mol/kg}$ i.p.). Potentially useful for the treatment of a broad range of disorders such as pain, Alzheimer's disease, Parkinson's disease, memory impairment, Tourette's syndrome, sleep disorders, attention deficit hyperactivity disorder, neurodegeneration, inflammation, amyotrophic lateral sclerosis, anxiety, depression, mania, schizophrenia, eating disorders, AIDS-induced dementia, epilepsy, urinary incontinence, Crohn's disease, migraine, erectile dysfunction and substance abuse and in smoking cessation. Other exemplified compounds from this series of 3-pyrrolidinyloxy-3'-pyridyl ether derivatives include the following:



Compound	R1	R2	R3	X	Formula
302662	1-Me-3-pyrrolidinyl-CH2	Br	Cl	tosylate	$\text{C}_{11}\text{H}_{14}\text{BrClN}_2\text{O} \cdot \text{C}_7\text{H}_8\text{O}_3\text{S}$
302663	3-pyrrolidinyl-CH2	Me	H		$\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$
302664	perhydro-3-azepinyl	H	Me	2HCl	$\text{C}_{12}\text{H}_{18}\text{N}_2\text{O} \cdot 2\text{HCl}$

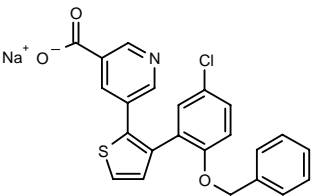
SOURCE – Abbott.

REFERENCES

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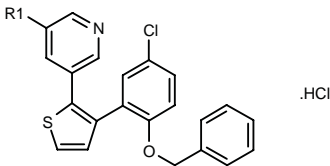
302931

5-[3-[2-(Benzyloxy)-5-chlorophenyl]thien-2-yl]pyridine-3-
carboxylic acid sodium salt



C23 H15 Cl N Na O3 S; Mol wt: 443.8845

ACTION – Analgesic, antipyretic and antiinflammatory agent with reduced adverse effects such as gastro-intestinal or renal toxicity, a prostaglandin E (PGE, EP) receptor ligand. Other exemplified compounds from this series of carboxylic acids and acylsulfonamides are:



Compound	R1	Formula
302932	CH2OH	$\text{C}_{23}\text{H}_{18}\text{ClNO}_2\text{S} \cdot \text{HCl}$
302933	CH(Me)2OH	$\text{C}_{26}\text{H}_{22}\text{ClNO}_2\text{S} \cdot \text{HCl}$
302934	CH(OH)CF3	$\text{C}_{24}\text{H}_{17}\text{ClF}_3\text{NO}_2\text{S} \cdot \text{HCl}$
302935	COCF3	$\text{C}_{24}\text{H}_{15}\text{ClF}_3\text{NO}_2\text{S} \cdot \text{HCl}$

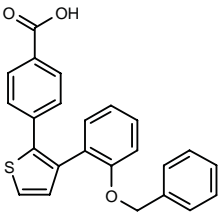
SOURCE – Merck Frosst.

REFERENCES

1. Lacombe, P. et al. (Merck Frosst Canada Inc.) Carboxylic acids and acylsulfonamides, compsns. containing such cpds. and methods of treatment. WO 0119819.

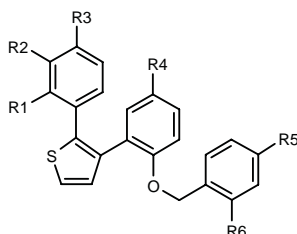
302936

4-[3-[2-(Benzyloxy)phenyl]thien-2-yl]benzoic acid



C24 H18 O3 S; Mol wt: 386.4692

ACTION – Analgesic, antipyretic and antiinflammatory agent with reduced adverse effects such as gastro-intestinal or renal toxicity, a prostaglandin E (PGE, EP) receptor ligand. Other specifically claimed compounds from this series of carboxylic acids and acylsulfonamides include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
302937	H	H	CH(OH)Me	H	H	H	C ₂₅ H ₂₂ O ₂ S
302938	H	2H-tetrazol-5-yl	H	Cl	H	H	C ₂₄ H ₁₇ ClN ₄ OS
302939	H	CH ₂ CO ₂ H	H	Cl	H	H	C ₂₅ H ₁₉ ClO ₃ S
302940	H	H	CO ₂ H	NO ₂	F	Cl	C ₂₄ H ₁₅ ClFNO ₅ S
302941	H	H	3-Pyr-CH ₂ -NHCO	NO ₂	F	Cl	C ₃₀ H ₂₁ ClFN ₃ O ₄ S
302943	Me	H	3-Pyr-CH ₂ -NHCO	Cl	F	Cl	C ₃₁ H ₂₃ Cl ₂ FN ₂ O ₂ S

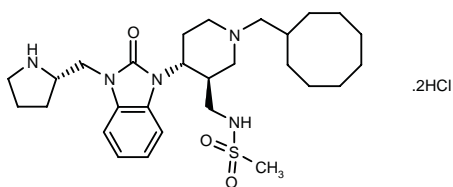
SOURCE – Merck Frosst.

REFERENCES

1. Lacombe, P. et al. (Merck Frosst Canada Inc.) *Carboxylic acids and acylsulfonamides, compsns. containing such cpds. and methods of treatment*. WO 0119814.

303565

N-[1-(Cyclooctylmethyl)-4(*R*)-[2-oxo-3-[pyrrolidin-2(*S*)-ylmethyl]-2,3-dihydro-1*H*-benzimidazol-1-yl]piperidin-3(*S*)-ylmethyl]methanesulfonamide dihydrochloride



C28 H45 N5 O3 S . 2HCl; Mol wt: 604.6833

ACTION – A representative compound from a series of sulfonamide derivatives that acts as an ORL1 (nociceptin, N/OFQ) receptor antagonist, as demonstrated by inhibition of [¹²⁵I]-Tyr¹⁴-nociceptin binding to human ORL1 receptors expressed in CHO cells (IC₅₀ = 0.86 nM) and antagonism of nociceptin-induced G-protein activation in these cells (IC₅₀ = 17 nM). This compound is potentially useful for the treatment of a broad range of diseases such as pain, obesity, Alzheimer's disease, schizophrenia, Parkinson's disease, depression, diabetes, polyuria and hypotension.

SOURCE – Banyu.

REFERENCES

1. Kawamoto, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Sulfonamide derivs.* JP 2001058991.

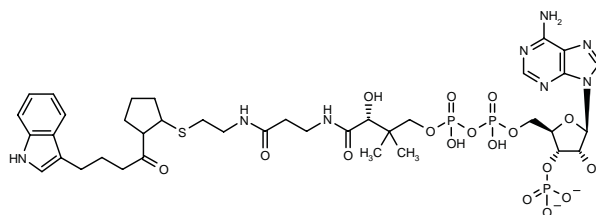
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

305382

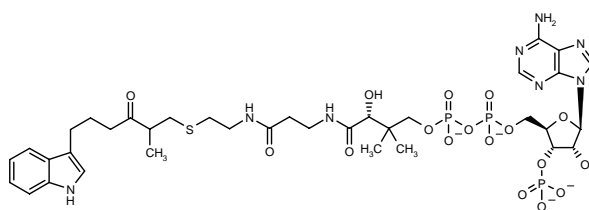
S-[2-[4-(1*H*-Indol-3-yl)butyryl]cyclopentyl]coenzyme A

3'-*O*-Phosphoadenosine-5'-diphosphoric acid 3(*R*)-hydroxy-3-[2-[2-[4-(1*H*-indol-3-yl)butyryl]cyclopentyl-sulfanyl]ethylcarbamoyl]ethylcarbamoyl]-2,2-dimethyl-propyl monoester



C38 H53 N8 O17 P3 S; Mol wt: 1018.8640

ACTION – Serotonin *N*-acetyltransferase inhibitor (K_i = 7 nM) potentially useful for the treatment of sleep and mood disorders. Another ketone analogue is:



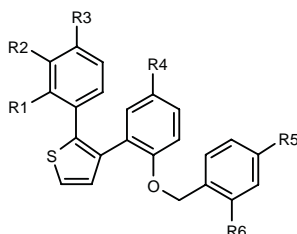
305381: C36 H49 N8 O17 P3 S

SOURCE – Johns Hopkins University, Baltimore, MD (US).

REFERENCES

1. Kim, C.M. and Cole, P.A. *Bisubstrate ketone analogues as serotonin N-acetyltransferase inhibitors*. J Med Chem 2001, 44(15): 2479.

ACTION – Analgesic, antipyretic and antiinflammatory agent with reduced adverse effects such as gastro-intestinal or renal toxicity, a prostaglandin E (PGE, EP) receptor ligand. Other specifically claimed compounds from this series of carboxylic acids and acylsulfonamides include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
302937	H	H	CH(OH)Me	H	H	H	C ₂₅ H ₂₂ O ₂ S
302938	H	2H-tetrazol-5-yl	H	Cl	H	H	C ₂₄ H ₁₇ ClN ₄ OS
302939	H	CH ₂ CO ₂ H	H	Cl	H	H	C ₂₅ H ₁₉ ClO ₃ S
302940	H	H	CO ₂ H	NO ₂	F	Cl	C ₂₄ H ₁₅ ClFNO ₅ S
302941	H	H	3-Pyr-CH ₂ -NHCO	NO ₂	F	Cl	C ₃₀ H ₂₁ ClFN ₃ O ₄ S
302943	Me	H	3-Pyr-CH ₂ -NHCO	Cl	F	Cl	C ₃₁ H ₂₃ Cl ₂ FN ₂ O ₂ S

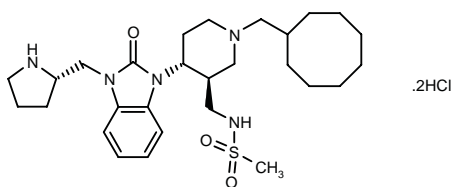
SOURCE – Merck Frosst.

REFERENCES

1. Lacombe, P. et al. (Merck Frosst Canada Inc.) *Carboxylic acids and acylsulfonamides, compsns. containing such cpds. and methods of treatment*. WO 0119814.

303565

N-[1-(Cyclooctylmethyl)-4(*R*)-[2-oxo-3-[pyrrolidin-2(*S*)-ylmethyl]-2,3-dihydro-1*H*-benzimidazol-1-yl]piperidin-3(*S*)-ylmethyl]methanesulfonamide dihydrochloride



C28 H45 N5 O3 S . 2HCl; Mol wt: 604.6833

ACTION – A representative compound from a series of sulfonamide derivatives that acts as an ORL1 (nociceptin, N/OFQ) receptor antagonist, as demonstrated by inhibition of [¹²⁵I]-Tyr¹⁴-nociceptin binding to human ORL1 receptors expressed in CHO cells (IC₅₀ = 0.86 nM) and antagonism of nociceptin-induced G-protein activation in these cells (IC₅₀ = 17 nM). This compound is potentially useful for the treatment of a broad range of diseases such as pain, obesity, Alzheimer's disease, schizophrenia, Parkinson's disease, depression, diabetes, polyuria and hypotension.

SOURCE – Banyu.

REFERENCES

1. Kawamoto, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Sulfonamide derivs.*. JP 2001058991.

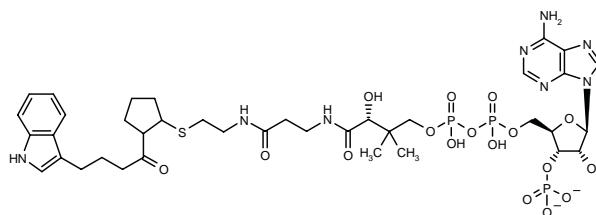
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

305382

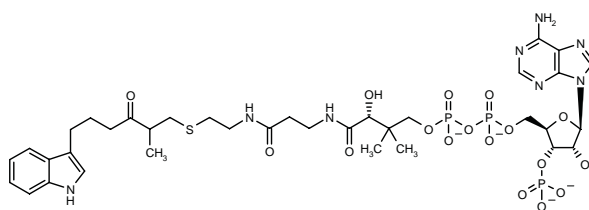
S-[2-[4-(1*H*-Indol-3-yl)butyryl]cyclopentyl]coenzyme A

3'-*O*-Phosphoadenosine-5'-diphosphoric acid 3(*R*)-hydroxy-3-[2-[2-[4-(1*H*-indol-3-yl)butyryl]cyclopentyl-sulfanyl]ethylcarbamoyl]ethylcarbamoyl]-2,2-dimethyl-propyl monoester



C38 H53 N8 O17 P3 S; Mol wt: 1018.8640

ACTION – Serotonin *N*-acetyltransferase inhibitor (K_i = 7 nM) potentially useful for the treatment of sleep and mood disorders. Another ketone analogue is:



305381: C36 H49 N8 O17 P3 S

SOURCE – Johns Hopkins University, Baltimore, MD (US).

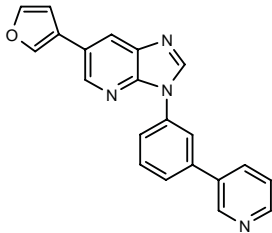
REFERENCES

1. Kim, C.M. and Cole, P.A. *Bisubstrate ketone analogues as serotonin N-acetyltransferase inhibitors*. J Med Chem 2001, 44(15): 2479.

ANXIOLYTICS

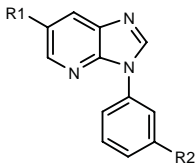
302393

6-(3-Furyl)-3-[3-(3-pyridyl)phenyl]-3*H*-imidazo[4,5-*b*]-pyridine



C21 H14 N4 O; Mol wt: 338.3686

ACTION – Anxiolytic agent and anticonvulsant with selective affinity for the α_2 and/or α_3 subunit of the human GABA_A receptor relative to the α_1 subunit; compound gave K_i values for displacement of [³H]-flumazenil from the α_2 and/or α_3 subunit of the human GABA_A receptor of 100 nM or less. Other specifically claimed compounds from this series of 3-phenylimidazo[4,5-*b*]pyridine derivatives are:



Compound	R1	R2	Formula
302394	3-furyl	2-oxo-1-pyrrolidinyl	C ₂₀ H ₁₆ N ₄ O ₂
302395	3-furyl	1-imidazolyl	C ₁₉ H ₁₃ N ₅ O
302396	3-furyl	4-morpholinyl-CH2	C ₂₁ H ₂₀ N ₄ O ₂
302397	Ph	3-Pyr	C ₂₃ H ₁₆ N ₄
302398	3-furyl	2-Ac-Ph	C ₂₄ H ₁₇ N ₃ O ₂
302399	3-furyl	2-CHO-Ph	C ₂₃ H ₁₅ N ₃ O ₂
302400	3-furyl	2-CN-Ph	C ₂₃ H ₁₄ N ₄ O
302402	3-furyl	2-CN-3-thienyl	C ₂₁ H ₁₂ N ₄ OS

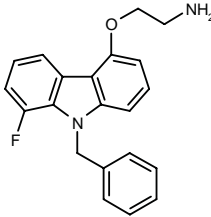
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Hallett, D.J. and Rowley, M. (Merck Sharp & Dohme Ltd.) *Imidazo-pyridine derivs. as ligands for GABA receptors*. WO 0118000.

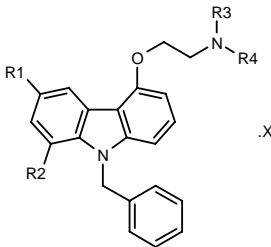
302569

2-(9-Benzyl-8-fluoro-9*H*-carbazol-4-yloxy)ethylamine



C21 H19 F N2 O; Mol wt: 334.3921

ACTION – 5-HT₆ receptor modulator (K_i = 2.4 nM against [³H]-LSD binding to human 5-HT₆ receptors cloned in HeLa cells), with potential for the treatment or prevention of a broad range of CNS disorders, particularly anxiety, obesity, depression, schizophrenia, stress-related diseases, panic disorder, phobia and obsessive-compulsive disorder. A representative compound from a series of aminoalkoxy carbazoles, wherein the following are also included:



Compound	R1	R2	R3	R4	X	Formula
302570	H	H	Me	H	fumarate	C ₂₂ H ₂₂ N ₂ O.C ₄ H ₄ O ₄
302571	H	H	-CH2CH2N(Me)CH2CH2-			C ₂₆ H ₂₉ N ₃ O
302572	Me	H	Me	H		C ₂₃ H ₂₄ N ₂ O
302575	H	F	Et	Et		C ₂₈ H ₂₇ N ₂ O

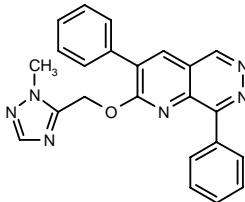
SOURCE – Pharmacia.

REFERENCES

1. Tenbrink, R.E. (Pharmacia Corp.) *Aminoalkoxy carbazoles for the treatment of CNS diseases*. WO 0117963.

302620

2-(1-Methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3,8-diphenyl-pyrido[2,3-*d*]pyridazine



C23 H18 N6 O; Mol wt: 394.4362

ACTION – A representative compound from a series of pyrido-pyridazine derivatives that acts as selective ligand for GABA_A receptors with good affinity for the α_2 and/or α_3 and/or α_5 subunit. Potential uses of this compound include the treatment of anxiety, epilepsy and cognition disorders.

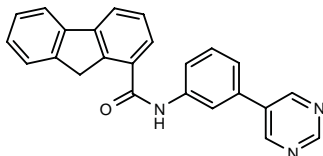
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Pyrido-pyridazine derivs. as ligands for GABA receptors*. WO 0118001.

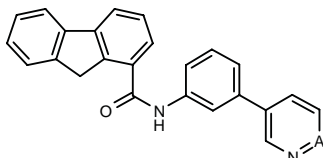
303426

N-[3-(5-Pyrimidinyl)phenyl]-9*H*-fluorene-1-carboxamide



C₂₄ H₁₇ N₃ O; Mol wt: 363.4183

ACTION – 5-HT antagonist, particularly active at 5-HT_{2C} receptors, as demonstrated by 92% inhibition of [³H]-mesulergine binding in rat prefrontal cortex preparations at 1 μM. This compound is potentially useful for the treatment of CNS disorders such as anxiety, depression, obsessive-compulsive disorders, migraine, anorexia, bulimia, Alzheimer's disease, sleep disorders, panic, withdrawal from drug abuse, schizophrenia, and spinal trauma- or head injury-related disorders. Other exemplified amides include the following:



Compound	A	Formula
303429	CH	C ₂₅ H ₁₈ N ₂ O
303430	N	C ₂₄ H ₁₇ N ₃ O

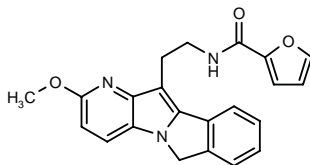
SOURCE – Fujisawa.

REFERENCES

1. Ito, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Amide cpds*. WO 0125229.

303564

N-[2-(2-Methoxy-6*H*-pyrido[2',3':4,5]pyrrolo[2,1-*a*]-isoindol-11-yl)ethyl]furan-2-carboxamide



C₂₂ H₁₉ N₃ O₃; Mol wt: 373.4101

ACTION – A polycyclic compound with affinity for melatonin receptors that is reported to have anxiolytic activity and potent effects on circadian rhythms via the melatonergic system. This compound is potentially useful for the treatment of seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity.

SOURCE – ADIR.

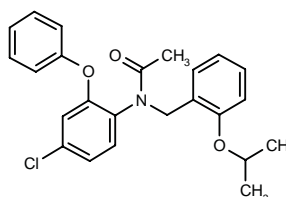
REFERENCES

1. Guillaumet, G. et al. (ADIR et Cie.) *Polycyclic azaindole derivs., process for their preparation and pharmaceutical compns. containing them*. EP 1092717, FR 2799757, JP 2001114781.

DAA-1097^{1,2,5,6}

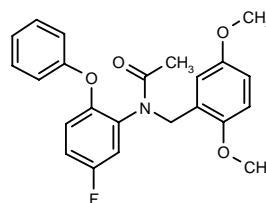
276271

N-(4-Chloro-2-phenoxyphenyl)-*N*-(2-isopropoxybenzyl)-acetamide



C₂₄ H₂₄ Cl N O₃; Mol wt: 409.9106

ACTION – Peripheral benzodiazepine receptor (PBR) agonist with subnanomolar affinity for PBR (IC₅₀ = 0.92 and 0.64 nM for displacement of [³H]-PK-11195 and [³H]-Ro-5-4864 binding, respectively), proven to be inactive at central benzodiazepine receptors and to have weak or negligible activity against several other receptors, neurotransmitters, ion channels and transporters. Oral administration of compound exerted anxiolytic activity in the mouse light/dark exploration test (0.03-0.1 mg/kg) and in the rat elevated plus-maze test (3 mg/kg). Unlike diazepam and buspirone, this compound did not affect spontaneous activity in mice and it increased hexobarbital sleeping time only at 100 mg/kg. In addition, compound activated steroidogenesis in Leydig tumor MA-10 cells and in mitochondrial preparations from MA-10 cells, glioma C6-2B cells and rat brain. Potentially useful as an anxiolytic agent. Another related compound is:



DAA-1106 [276272]:¹⁻⁶ C₂₃ H₂₂ F N O₄

SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.; Nihon Nohyaku Co., Ltd.) *Aryloxyaniline derivs*. EP 1004573, JP 1999171844, WO 9906353.

2. Culty, M. et al. *Peripheral benzodiazepine receptor binding properties and effects on steroid synthesis of two new phenoxyphenyl-acetamide derivatives, DAA1097 and DAA1106*. Drug Dev Res 2001, 52(3): 475.

3. Chaki, S. et al. *Binding characteristics of [3D]DAA1106, a novel and selective ligand for peripheral benzodiazepine receptors*. Eur J Pharmacol 1999, 371(2-3): 197.

4. Chaki, S. et al. *DAA1106, a potent and selective agonist for peripheral benzodiazepine receptors*. Soc Neurosci Abst 1999, 25(Part 1): Abst 172.23.

5. Okuyama, S. et al. *Neuropharmacological profile of peripheral benzodiazepine receptor agonists, DAA1097 and DAA1106*. Life Sci 1999, 64(16): 1455.

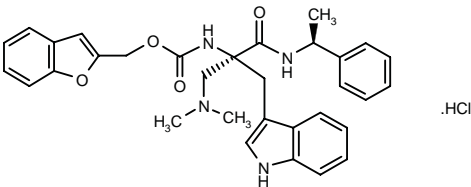
6. Yoshikawa, R. et al. *Neuropharmacological profile of peripheral benzodiazepine receptor agonists, DAA1097 and DAA1106*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-454.

PD-174424²

305287

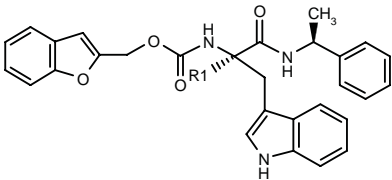
*N*²-(1-Benzofuran-2-ylmethoxycarbonyl)- α -(dimethylaminomethyl)-*N*¹-[1(*S*)-phenylethyl]-*D*-tryptophanamide hydrochloride

N-[1(*S*)-(Dimethylaminomethyl)-2-(1*H*-indol-3-yl)-1-[*N*-[1(*S*)-phenylethyl]carbamoyl]ethyl]carbamic acid benzo-furan-2-ylmethyl ester hydrochloride



C32 H34 N4 O4 . HCl; Mol wt: 575.1055

ACTION – Tachykinin NK₁ receptor antagonist with subnanomolar affinity for human NK₁ receptors (IC₅₀ = 0.46 nM), high selectivity over NK₂ receptors (IC₅₀ = 671 nM) and no activity at human NK₃ receptors. Compound showed good brain penetration and good efficacy in the gerbil foot-tapping paradigm, where it antagonized the foot-tapping response to substance P with a minimum effective dose (MED) of 1 mg/kg s.c. Potentially useful as an anxiolytic and antidepressant. Other related compounds are:



Compound	R1	Formula
PD-160226 [305601] ^{1,2}	H	C ₂₉ H ₂₇ N ₃ O ₄
PD-170541 [305605] ²	Et	C ₃₁ H ₃₁ N ₃ O ₄
PD-207746 [305606] ²	Pr	C ₃₂ H ₃₃ N ₃ O ₄
PD-307496 [305607] ²	i-Bu	C ₃₃ H ₃₅ N ₃ O ₄
PD-170540 [305609] ²	CH ₂ OMe	C ₃₁ H ₃₁ N ₃ O ₅

SOURCE – Pfizer.

REFERENCES

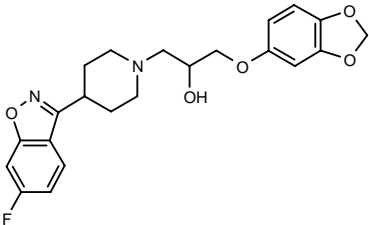
1. Horwell, D.C. et al. (Pfizer Inc.) *Tachykinin antagonists*. EP 0655055, EP 1000930, US 5594022, WO 9404494.

2. Ashwood, V.A. et al. *Utilization of an intramolecular hydrogen bond to increase the CNS penetration of an NK1 receptor antagonist*. J Med Chem 2001, 44(14): 2276.

ANTIPSYCHOTIC DRUGS

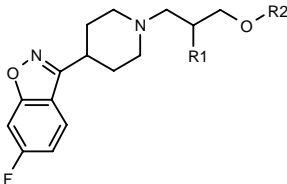
302465

1-(1,3-Benzodioxol-5-yloxy)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propan-2-ol

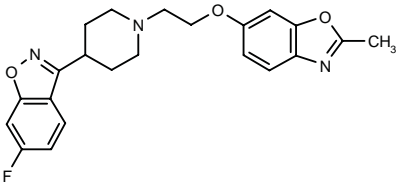


C22 H23 F N2 O5; Mol wt: 414.4307

ACTION – Psychotropic agent that displays effects characteristic of atypical neuroleptic agents together with anxiolytic and psychosedative activity. Compound was shown to inhibit the learned conditioned avoidance response (CAR) in rats with an ID₅₀ value of 1.0 mg/kg p.o., being more potent than chlorpromazine and clozapine (ID₅₀ = 13.2 and 21.3 mg/kg p.o., respectively). In addition, it inhibited apomorphine-induced climbing (ID₅₀ = 0.2 mg/kg p.o. vs. 6.8 and 35.4 mg/kg p.o. for chlorpromazine and clozapine, respectively) more potently than apomorphine-induced stereotypy (ED₅₀ = 1.4 mg/kg p.o. vs. 6.1 and 11.8 mg/kg p.o. for chlorpromazine and clozapine, respectively) in mice, and is thus expected to exhibit a lower liability for extrapyramidal side effects, and it further inhibited DOI-induced hyperthermia in rats (MED = 1.0 mg/kg p.o.). Other exemplified compounds from this series of alkylpiperidinybenzo[d]-isoxazole derivatives include the following:



Compound	R1	R2	Formula
302468	H	1,3-benzodioxol-5-yl	C ₂₂ H ₂₃ FN ₂ O ₄
302472	OH	2-Me-6-benzoxazolyl	C ₂₃ H ₂₄ FN ₃ O ₄
302476	H	2-Me-6-benzoxazolyl	C ₂₃ H ₂₄ FN ₃ O ₃
302477	OH	2-Me-5-benzoxazolyl	C ₂₃ H ₂₄ FN ₃ O ₄
302480	OH	1-Naph	C ₂₅ H ₂₅ FN ₂ O ₃
302481	OH	2-MeO-Ph	C ₂₂ H ₂₅ FN ₂ O ₄



302479: C22 H22 F N3 O3

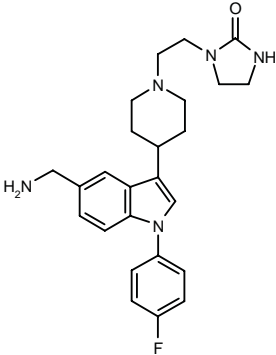
SOURCE – Egis.

REFERENCES

1. Barkóczy, J. et al. (Egis Pharmaceuticals Ltd.) *Alkylpiperidinybenzo[d]isoxazole derivs. having psychotropic activity, pharmaceutical compsns. containing the same, and a process for the preparation of the active ingredient.* WO 0117993.

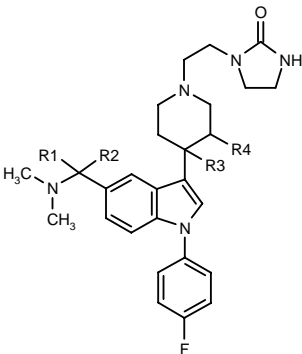
303045

1-[2-[4-[5-(Aminomethyl)-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]imidazolidin-2-one



C25 H30 F N5 O; Mol wt: 435.5440

ACTION – Potent and selective α_1 -adrenoceptor antagonist, as demonstrated in binding assays by IC_{50} values of 0.49, 180 and 84 nM, respectively, against [3H]-prazosin binding to α_1 -adrenoceptors in rat brain, [3H]-ketanserin binding to 5-HT $_{2A}$ receptors in rat cortex and [3H]-spiperone binding to dopamine D2 receptors in rat corpus striatum; respective IC_{50} values for sertindole and prazosin were 3.4, 4.1 and 0.39 nM, and 0.36, 11,000 and 3300 nM. Potentially useful for the treatment of psychosis, mania, benign prostatic hyperplasia, hypertension, cardiac arrhythmias and elevated intraocular pressure. The corresponding labeled compound is reported to be useful as a PET (positron emission tomography) or SPECT (single photon emission computed tomography) ligand. Other exemplified compounds from this series of 5-aminoalkyl and 5-aminocarbonyl substituted indoles include the following:



Compound	R1	R2	R3	R4	Formula
303047		-O-	H	H	C ₂₇ H ₃₂ FN ₅ O ₂
303048	H	H	H	H	C ₂₇ H ₃₄ FN ₅ O
303049	H	H	bond		C ₂₇ H ₃₂ FN ₅ O

SOURCE – Lundbeck.

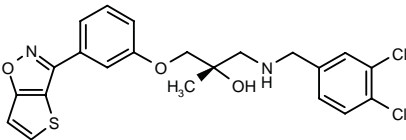
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MDL-813272

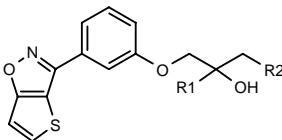
302889

1-(3,4-Dichlorobenzylamino)-2(*S*)-methyl-3-[3-(thieno[2,3-*d*]isoxazol-3-yl)phenoxy]propan-2-ol



C22 H20 Cl2 N2 O3 S; Mol wt: 463.3830

ACTION – Dopamine D4 receptor antagonist, as demonstrated by a K_i value of 0.013 μM against [3H]-spiperone binding in HEK298 cells stably transfected with the human D4 receptor. *In vivo*, compound was shown to antagonize MK-801-induced stereotypy in mice (62.5% inhibition at 20 mg/kg p.o.). Potentially useful for the treatment of D4 receptor-mediated disorders such as attention deficit hyperactivity disorder, obsessive–compulsive disorder, psychoses, substance abuse and dependence, Parkinson’s disease, tardive dyskinesia, Tourette’s syndrome, etc. Other exemplified compounds from this series of thienoisoxazolyl- and thienylpyrazolyl-phenoxy substituted propyl derivatives include the following:



Compound	R1	R2	Isomer	Formula
MDL-813088 [302890]	H	4-(2-CN-Ph)-1-Piz	R	C ₂₈ H ₂₄ N ₄ O ₃ S
MDL-812684 [302891]	Me	NHCH2Ph	S	C ₂₂ H ₂₂ N ₂ O ₃ S
MDL-813268 [302893]	Me	2-F-PhCH2NH	S	C ₂₂ H ₂₁ FN ₂ O ₃ S
MDL-813271 [302895]	Me	2-Cl-PhCH2NH	S	C ₂₂ H ₂₁ ClN ₂ O ₃ S
MDL-813277 [302896]	Me	4-MeO-PhCH2NH	S	C ₂₃ H ₂₄ N ₂ O ₄ S
MDL-813281 [302897]	Me	3-thienyl-CH2NH	S	C ₂₀ H ₂₀ N ₂ O ₃ S ₂
MDL-813307 [302898]	H	4-(6-F-1,2-benz-isothiazol-3-yl)-1-Pip	R	C ₂₆ H ₂₄ FN ₃ O ₃ S ₂
MDL-813309 [302900]	H	4-(2-pyrimidinyl)-1-Piz	R	C ₂₂ H ₂₃ N ₅ O ₃ S
MDL-812828 [302956]	H	4-(2-MeO-Ph)-1-Piz	R	C ₂₈ H ₂₇ N ₃ O ₄ S

SOURCE – Aventis Pharma.

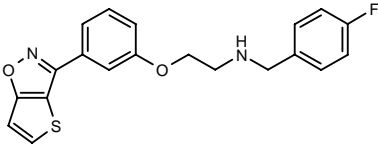
REFERENCES

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MDL-813728

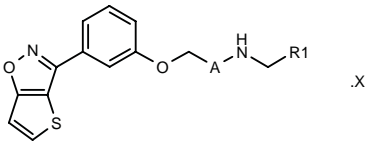
302847

N-(4-Fluorobenzyl)-*N*-[2-[3-(thieno[2,3-*d*]isoxazol-3-yl)phenoxy]ethyl]amine



C20 H17 F N2 O2 S; Mol wt: 368.4303

ACTION – Dopamine D4 receptor antagonist, as demonstrated by a K_i value of 0.012 μM against [^3H]-spiperone binding in HEK298 cells stably transfected with the human D4 receptor. *In vivo*, compound was shown to antagonize MK-801-induced stereotypy in mice with an ED_{50} value of 14.14 mg/kg p.o. Potentially useful for the treatment of D4 receptor-mediated disorders such as attention deficit hyperactivity disorder, obsessive–compulsive disorder, psychoses, substance abuse and dependence, Parkinson’s disease, tardive dyskinesia, Tourette’s syndrome, etc. Other exemplified compounds from this series of thienoisoxazole phenoxy unsubstituted ethyl and propyl derivatives include the following:



Compound	R1	A	X	Formula
MDL-813221 [302848]	Ph	-(CH2)2-		C ₂₁ H ₂₀ N ₂ O ₂ S
MDL-813519 [302850]	4-F-Ph	-(CH2)2-		C ₂₁ H ₁₉ FN ₂ O ₂ S
MDL-813523 [302851]	3-thienyl	-(CH2)2-		C ₁₉ H ₁₈ N ₂ O ₂ S ₂
MDL-813644 [302852]	Ph	-CH2-		C ₂₀ H ₁₈ N ₂ O ₂ S
MDL-813731 [302853]	4-Me-Ph	-CH2-		C ₂₁ H ₂₀ N ₂ O ₂ S
MDL-813734 [302854]	3-thienyl	-CH2-		C ₁₈ H ₁₆ N ₂ O ₂ S ₂
MDL-814008 [302856]	Ph	-CH2-	HCl	C ₂₀ H ₁₈ N ₂ O ₂ S.HCl
MDL-814009 [302857]	3-F-Ph	-CH2-		C ₂₀ H ₁₇ FN ₂ O ₂ S

SOURCE – Aventis Pharma.

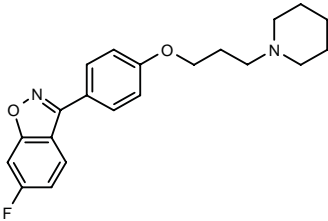
REFERENCES

1. Lee, G.E. et al. (Aventis Pharmaceuticals, Inc.) *Thienoisoxazole phenoxy unsubstd. ethyl and propyl derivs. useful as D 4 antagonists*. WO 0119832.

MDL-814608A

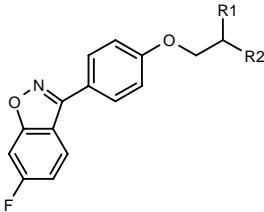
302864

6-Fluoro-3-[4-[3-(1-piperidiny)propoxy]phenyl]-1,2-benzisoxazole



C21 H23 F N2 O2; Mol wt: 354.4227

ACTION – Dopamine D4 receptor antagonist, as demonstrated by a K_i value of 0.00697 μM against [^3H]-spiperone binding in HEK298 cells stably transfected with the human D4 receptor. *In vivo*, compound was shown to antagonize MK-801-induced stereotypy in mice with an ED_{50} value of 3.11 mg/kg p.o. Potentially useful for the treatment of D4 receptor-mediated disorders such as attention deficit hyperactivity disorder, obsessive–compulsive disorder, psychoses, substance abuse and dependence, Parkinson’s disease, tardive dyskinesia, Tourette’s syndrome, etc. Other exemplified compounds from this series of benzisoxazolyl-, pyridoisoaxazolyl- and benzothienyl-phenoxy derivatives include the following:



Compound	R1	R2	Isomer	Formula
MDL-81440 [302866]	OH	4-Ph-1-Pip-CH2	R	C ₂₇ H ₂₇ FN ₂ O ₃
MDL-813751 [302870]	OH	1,2,3,4-tetrahydro-isoquinolin-2-yl-CH2	S	C ₂₅ H ₂₃ FN ₂ O ₃
MDL-814300 [302872]	OH	CH2NHCH2Ph	R	C ₂₃ H ₂₁ FN ₂ O ₃
MDL-813848 [302874]	OH	2-F-PhCH2NHCH2	R	C ₂₃ H ₂₀ F ₂ N ₂ O ₃
MDL-813866 [302876]	OH	3-thienyl-CH2NHCH2	S	C ₂₁ H ₁₉ FN ₂ O ₃ S
MDL-814139 [302878]	H	1-Pip		C ₂₀ H ₂₁ FN ₂ O ₂
MDL-814252 [302879]	H	CH2NHCH2Ph		C ₂₃ H ₂₁ FN ₂ O ₂
MDL-814607 [302881]	H	1-pyrrolidiny-CH2		C ₂₀ H ₂₁ FN ₂ O ₂
MDL-814701 [302883]	H	cyclohexyl-CH2NH		C ₂₂ H ₂₅ FN ₂ O ₂
MDL-814967 [302884]	H	4-Me-1-Pip-CH2		C ₂₂ H ₂₅ FN ₂ O ₂

SOURCE – Aventis Pharma.

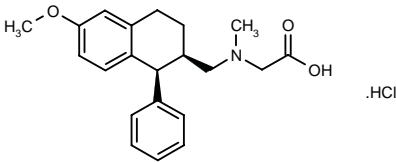
REFERENCES

1. Shutske, G.M. et al. (Aventis Pharmaceuticals, Inc.) *Benzisoxazolyl-, pyridoisoaxazolyl- and benzothienyl-phenoxy derivs. useful as D4 antagonists*. WO 0119821.

ORG-25935

305119

cis-*N*-(6-Methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-ylmethyl)-*N*-methylglycine hydrochloride



C21 H25 N O3 . HCl; Mol wt: 375.8934

ACTION – Glycine reuptake inhibitor with high affinity for the GlyT-1 transporter, able to dose-dependently increase extracellular glycine levels in striatum (35, 80 and 130% increase above basal levels at 3, 6 and 10 mg/kg i.p., respectively), frontal cortex and hippocampus (75 and 70% increase, respectively, at 6 mg/kg i.p.) of freely moving rats. Potentially useful for the treatment of schizophrenia.

SOURCE – Organon.

REFERENCES

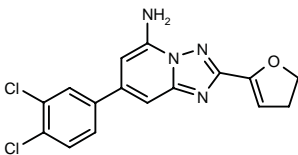
1. Gibson, S.G. et al. (Akzo Nobel N.V.) *Aminomethylcarboxylic acid derivs.* EP 1100769, WO 0007978.

2. Ge, J. et al. *The effects of Org 25935 on the extracellular levels of glycine in brain regions of freely moving rats.* Br J Pharmacol 2001, 133(Suppl.): Abst 135P.

TREATMENT OF MOOD DISORDERS

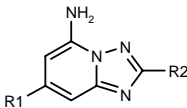
302515

7-(3,4-Dichlorophenyl)-2-(4,5-dihydrofuran-2-yl)[1,2,4]-triazolo[1,5-a]pyridin-5-amine



C16 H12 Cl2 N4 O; Mol wt: 347.2038

ACTION – Adenosine receptor ligand that exhibited adenosine A_{2A} receptor-antagonist activity in CHO cells expressing this receptor (pK_i = 8.1). This compound is preferably indicated for the treatment of depression and Parkinson's disease, as well as for use as a neuroprotectant. Other exemplified amino-triazolopyridine derivatives are:



Compound	R1	R2	Formula
302516	3-Me-Ph	4,5-dihydro-2-furyl	C ₁₇ H ₁₆ N ₄ O
302517	2-Me-4-Pyr	2-Pyr	C ₁₇ H ₁₄ N ₆
302518	3-F-Ph	4,5-dihydro-2-furyl	C ₁₆ H ₁₃ FN ₄ O
302519	3,4-(MeO)2-Ph	2-furyl	C ₁₈ H ₁₆ N ₄ O ₃
302520	2-F-4-Pyr	2-furyl	C ₁₅ H ₁₀ FN ₅ O
302521	6-MeO-3-Pyr	2-furyl	C ₁₈ H ₁₃ N ₅ O ₂
302522	3-Me-Ph	2-furyl	C ₁₇ H ₁₄ N ₄ O
302523	2-Et-4-Pyr	2-Pyr	C ₁₈ H ₁₆ N ₆

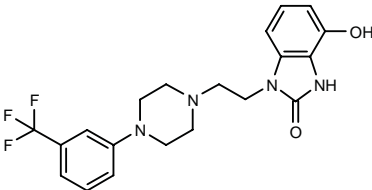
SOURCE – Roche.

REFERENCES

1. Huber Trottmann, G. et al. (F. Hoffmann-La Roche AG) *Amino-triazolopyridine derivs..* WO 0117999.

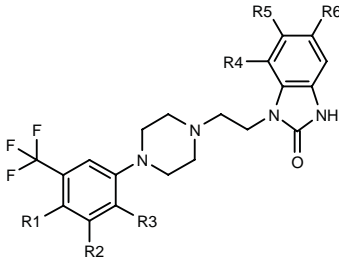
303165

4-Hydroxy-1-[2-[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]ethyl]-2,3-dihydro-1*H*-benzimidazol-2-one



C20 H21 F3 N4 O2; Mol wt: 406.4059

ACTION – Agent for the treatment of CNS disorders such as depression, schizophrenia, Parkinson's disease, anxiety, sleep disorders, sexual disorders and age-related memory impairment with high affinity for 5-HT_{1A}, 5-HT_{2A} and dopamine D4 receptors, as demonstrated in binding assays by K_i values of 15.4, 43.8 and 33.9 nM, respectively, for 5-HT_{1A} (rat hippocampus), 5-HT_{2A} (rat cortex) and D4 (CHO cells expressing human receptor) receptors. Other specifically claimed compounds from this series of benzimidazolone derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
303166	H	H	H	H	OH	H	C ₂₀ H ₂₁ F ₃ N ₄ O ₂
303167	H	H	H	H	H	OH	C ₂₀ H ₂₁ F ₃ N ₄ O ₂
303168	H	H	H	OH	H	H	C ₂₀ H ₂₁ F ₃ N ₄ O ₂
303169	OH	H	H	H	H	H	C ₂₀ H ₂₁ F ₃ N ₄ O ₂
303170	H	OH	H	H	H	H	C ₂₀ H ₂₁ F ₃ N ₄ O ₂
303171	H	H	OH	H	H	H	C ₂₀ H ₂₁ F ₃ N ₄ O ₂

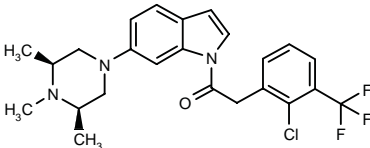
SOURCE – Boehringer Ingelheim.

REFERENCES

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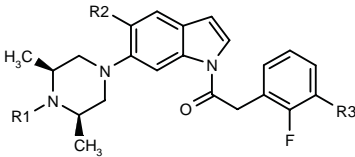
303309

cis-2-[2-Chloro-3-(trifluoromethyl)phenyl]-1-[6-(3,4,5-trimethylpiperazin-1-yl)indol-1-yl]ethanone

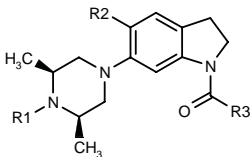


C24 H25 Cl F3 N3 O; Mol wt: 463.9285

ACTION – 5-HT_{1B} antagonist that is expected to be useful for the treatment of CNS disorders, particularly depression. Other specifically claimed piperazine derivatives are:



Compound	R1	R2	R3	Formula
303310	Me	OMe	CF3	C ₂₅ H ₂₇ F ₄ N ₃ O ₂
303313	H	OMe	Cl	C ₂₃ H ₂₅ ClFN ₃ O ₂
303314	Me	F	CF3	C ₂₄ H ₂₄ F ₅ N ₃ O



Compound	R1	R2	R3	Formula
303311	H	OMe	2,3-(Cl)2-PhCH2	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂
303312	H	OMe	4-[2-Me-6-(2-oxo-1-pyrrolidinyl)-3-Pyr]-Ph	C ₃₂ H ₃₇ N ₅ O ₃
303315	Me	Me	3-CF3-2-Cl-PhNH	C ₂₄ H ₂₈ ClF ₃ N ₄ O

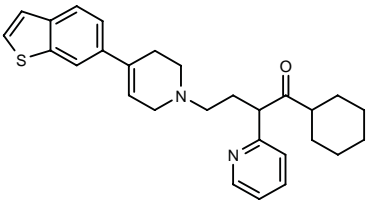
SOURCE – GlaxoSmithKline.

REFERENCES

1. Marshall, H. et al. (SmithKline Beecham plc) *Piperazine derivs. as 5-HT_{1B} antagonists*. WO 0123374.

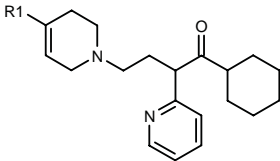
303354

4-[4-(6-Benzothienyl)-1,2,3,6-tetrahydropyridin-1-yl]-1-cyclohexyl-2-(2-pyridyl)butan-1-one



C28 H32 N2 O S; Mol wt: 444.6398

ACTION – Antidepressant, a 5-HT reuptake inhibitor and 5-HT_{1A} and/or 5-HT_{2A} receptor antagonist. This compound is also potentially useful for the treatment of anxiety, nicotine withdrawal, hypertension, cognition disorders, psychosis, sleep disorders, migraine, eating disorders and obsessive–compulsive disorder, among others. Other specifically claimed piperidine derivatives are:



Compound	R1	Formula
303355	5-benzothienyl	C ₂₈ H ₃₂ N ₂ OS
303356	2-benzothienyl	C ₂₈ H ₃₂ N ₂ OS
303357	3-benzothienyl	C ₂₈ H ₃₂ N ₂ OS

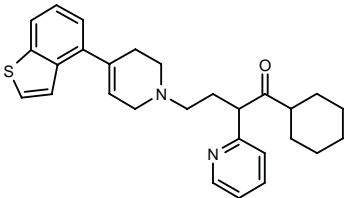
SOURCE – Lilly.

REFERENCES

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303359

4-[4-(4-Benzothienyl)-1,2,3,6-tetrahydropyridin-1-yl]-1-cyclohexyl-2-(2-pyridyl)butan-1-one



C28 H32 N2 O S; Mol wt: 444.6398

ACTION – Antidepressant, a 5-HT reuptake inhibitor and 5-HT_{1A} and/or 5-HT_{2A} receptor antagonist. This compound is also potentially useful for the treatment of anxiety, nicotine withdrawal, hypertension, cognition disorders, psychosis, sleep disorders, migraine, eating disorders and obsessive–compulsive disorder, among others.

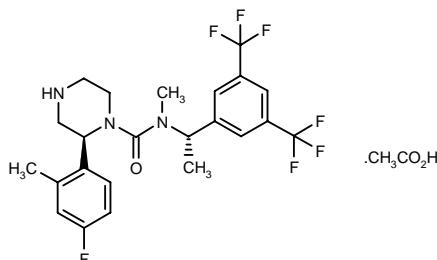
SOURCE – Lilly.

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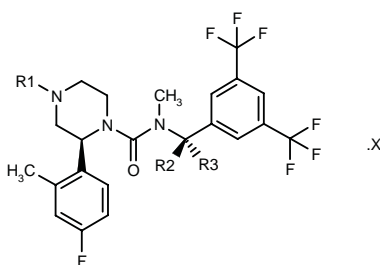
303434

N-[1(*S*)-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-2(*S*)-(4-fluoro-2-methylphenyl)-*N*-methylpiperazine-1-carboxamide acetate



C23 H24 F7 N3 O . C2 H4 O2; Mol wt: 551.5002

ACTION – NK₁ receptor antagonist (pK_i = 9.27 against [³H]-substance P binding to recombinant human NK₁ receptors expressed in CHO cells), proven to inhibit hind foot tapping induced by the NK₁ agonist δ -aminovaleryl⁶-[Pro⁹,Me-Leu¹⁰]-substance P(7-11) in gerbils with an ID₅₀ value of 0.04 mg/kg p.o. when administered 1 h prior to the agonist. Potentially useful for the treatment of pain, sleep disorders, depression, anxiety, panic disorders, cognitive disorders, drug dependence, inflammatory disorders, allergic disorders, emesis and gastrointestinal disorders, particularly depressive disorders, anxiety and panic disorders. Within this series of piperazine derivatives, the following compounds are also included:



Compound	R1	R2	R3	X	Formula
303435	COCH2NH2	H	H	HCl	C ₂₄ H ₂₆ F ₇ N ₄ O ₂ ·HCl
303436	H	Me	Me	HCl	C ₂₄ H ₂₆ F ₇ N ₃ O·HCl
303437	H	Me	H	MeSO3H	C ₂₃ H ₂₄ F ₇ N ₃ O·CH ₄ O ₃ S

SOURCE – GlaxoSmithKline.

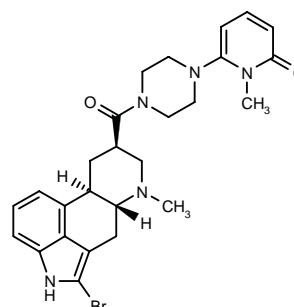
REFERENCES

1. Alvaro, G. et al. (Glaxo Group Ltd.) *Chemical cpds*. WO 0125219.

303523

6-[4-[(6*aR*,9*R*,10*aR*)-5-Bromo-7-methyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinolin-9-ylcarbonyl]-piperazin-1-yl]-1-methylpyridin-2(1*H*)-one

6-[4-[(8 β)-2-Bromo-6-methylergolin-8-ylcarbonyl]piperazin-1-yl]-1-methylpyridin-2(1*H*)-one



C26 H30 Br N5 O2; Mol wt: 524.4600

ACTION – A selective antagonist at the somatostatin sst₁ receptor that exhibited high affinity for native rat, native human and recombinant human sst₁ receptors (pIC₅₀ = 9.7, 9.0 and 8.8, respectively). This compound reduced aggressive behavior and reversed social withdrawal in experimental tests in mice at 3-30 mg/kg p.o. Preferred indications for the compounds of this invention are depression, anxiety, bipolar disorders and attention deficit hyperactivity disorder.

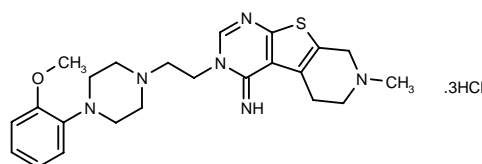
SOURCE – Novartis.

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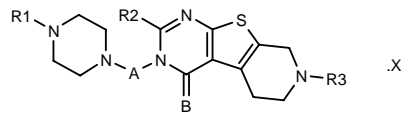
303524

3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-7-methyl-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-*d*]-pyrimidin-4-imine trihydrochloride



C23 H30 N6 O S . 3HCl; Mol wt: 547.9797

ACTION – A representative compound from a series of 3-substituted pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine derivatives with 5-HT_{1A} and 5-HT_{1B} receptor-antagonist activity. Potentially useful for the treatment of depression and related disorders such as seasonal affective disorder, anxiety, panic attacks, obsessive-compulsive disorder, memory disturbances and psychogenic eating disorders such as anorexia and bulimia. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	B	X	Formula
303525	2-MeO-Ph	H	Me	-(CH2)2-	O	3HCl	C ₂₃ H ₂₉ N ₅ O ₂ S .3HCl
303526	2-MeO-Ph	H	4-Cl-Ph- -CH2	-(CH2)2-	O	3HCl	C ₂₉ H ₃₂ ClN ₅ O ₂ S .3HCl
303530	2-MeO-Ph	H	Me	-(CH2)3-	O	.3HCl .2H2O	C ₂₄ H ₃₁ N ₅ O ₂ S .3HCl.2H ₂ O
303532	2-Pyr	H	Me	-(CH2)3-	NH	.4HCl .H2O	C ₂₂ H ₂₉ N ₇ S .4HCl.H ₂ O
303533	2-Pyr	H	Me	-(CH2)2-	O	.3HCl .2H2O	C ₂₁ H ₂₆ N ₆ OS .3HCl.2H ₂ O
303537	1-Naph	H	Me	-CH2CH(Me)-	O	.3HCl .2H2O	C ₂₇ H ₃₁ N ₆ OS .3HCl.2H ₂ O
303542	2-MeO-Ph	H	Me	-CH(Me)CH2-	O	3HCl	C ₂₄ H ₃₁ N ₅ O ₂ S .3HCl
303543	2-MeO-Ph	Me	Me	-(CH2)2-	O		C ₂₄ H ₃₁ N ₅ O ₂ S
303544	2-MeO-Ph	OH	Ac	-(CH2)2-	O		C ₂₄ H ₂₉ N ₅ O ₄ S
303545	2-MeO-Ph	H	Ac	-(CH2)2-	O		C ₂₄ H ₂₉ N ₅ O ₃ S
303546	2-MeO-Ph	H	H	-(CH2)2-	O		C ₂₂ H ₂₇ N ₅ O ₂ S
303547	2-MeO-Ph	H	1-Naph- -CH2CH2	-(CH2)2-	O	3HCl	C ₃₄ H ₃₇ N ₅ O ₂ S .3HCl

SOURCE – BASF.

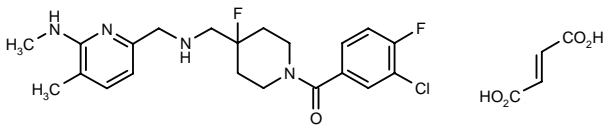
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1. Steiner, G. et al. (BASF AG) 3-Substd. pyrido[4',3':4,5]thieno[2,3-d]pyrimidine derivs., their preparation and their use. DE 19636769, US 6222034, WO 9811110.

F-13714*

265523

1-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-[5-methyl-6-(methylamino)pyridin-2-ylmethylaminomethyl]piperidine fumarate



C21 H25 Cl F2 N4 O . C4 H4 O4; Mol wt: 538.9761

ACTION – High-affinity and selective ligand for the 5-HT_{1A} receptor (pK_i = 10.23, 5.89 and 7.17 for 5-HT_{1A} and dopamine D2 receptors and α₁-adrenoceptors, respectively) with functional agonist activity *in vitro* in HA7 cells expressing 5-HT_{1A} receptors (pEC₅₀ = 8.70 for blockade of forskolin-stimulated cAMP). *In vivo*, compound exhibited 5-HT_{1A} receptor-agonist activity, evaluated as the ability to induce lower lip retraction in mice (ED₅₀ = 0.02 and 0.08 mg/kg i.p. and p.o., respectively), which correlated well with its antidepressant-like activity in the forced swimming test in mice (ED₅₀ = 0.065 mg/kg p.o.).

SOURCE – Pierre Fabre (bioMérieux-Pierre Fabre).

REFERENCES

1. Vacher, B. et al. (Pierre Fabre Médicament) Pyridin-2-yl-methylamine derivs., method of preparing and application as medicine. EP 0946546, JP 2001504129, US 6020345, WO 9822459.

2. Koek, W. et al. 5-HT_{1A} receptor activation and antidepressant-like effects: F 13714 has high efficacy and marked antidepressant potential. Eur J Pharmacol 2001, 420(2-3): 103.

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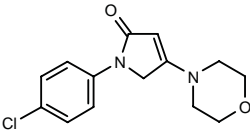
*Identified compound **265523** Drug Data Rep 1998, 020(09): 0753.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

302616

1-(4-Chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-pyrrol-2-one



C14 H15 Cl N2 O2; Mol wt: 278.7375

ACTION – Anticonvulsant and anxiolytic agent with a low liability to cause side effects. *In vivo*, compound protected rats against convulsions induced by maximal electroshock (ED₅₀ = 19 mg/kg p.o.) or pentylenetetrazol (ED₅₀ = 11 mg/kg p.o.), while displaying low neurotoxicity (NT₅₀ > 500 mg/kg p.o.). In addition, it exhibited anxiolytic effects in the Vogel conflict test in rats and in the elevated plus-maze model in mice at a dose of 10 mg/kg p.o. A representative compound from a series of 4-amino-1-aryl-1,5-dihydro-pyrrol-2-one derivatives.

SOURCE – Arzneimittelwerk Dresden.

REFERENCES

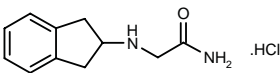
1. Arnold, T. et al. (Arzneimittelwerk Dresden GmbH) 4-Amino-1-aryl-1,5-dihydro-pyrrole-2-one with anti-convulsive and anxiolytic properties and a method for producing the same. DE 19944332, WO 0119793.

CHF-3381

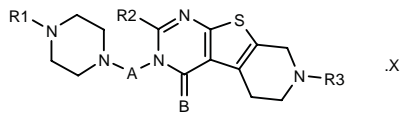
300377

N-(2-Indanyl)glycinamide hydrochloride

2-(2,3-Dihydro-1H-inden-2-ylamino)acetamide hydrochloride



C11 H14 N2 O . HCl; Mol wt: 226.7055



Compound	R1	R2	R3	A	B	X	Formula
303525	2-MeO-Ph	H	Me	-(CH2)2-	O	3HCl	C ₂₃ H ₂₉ N ₅ O ₂ S .3HCl
303526	2-MeO-Ph	H	4-Cl-Ph- -CH2	-(CH2)2-	O	3HCl	C ₂₉ H ₃₂ ClN ₅ O ₂ S .3HCl
303530	2-MeO-Ph	H	Me	-(CH2)3-	O	.3HCl .2H2O	C ₂₄ H ₃₁ N ₅ O ₂ S .3HCl.2H ₂ O
303532	2-Pyr	H	Me	-(CH2)3-	NH	.4HCl .H2O	C ₂₂ H ₂₉ N ₇ S .4HCl.H ₂ O
303533	2-Pyr	H	Me	-(CH2)2-	O	.3HCl .2H2O	C ₂₁ H ₂₆ N ₆ OS .3HCl.2H ₂ O
303537	1-Naph	H	Me	-CH2CH(Me)-	O	.3HCl .2H2O	C ₂₇ H ₃₁ N ₆ OS .3HCl.2H ₂ O
303542	2-MeO-Ph	H	Me	-CH(Me)CH2-	O	3HCl	C ₂₄ H ₃₁ N ₅ O ₂ S .3HCl
303543	2-MeO-Ph	Me	Me	-(CH2)2-	O		C ₂₄ H ₃₁ N ₅ O ₂ S
303544	2-MeO-Ph	OH	Ac	-(CH2)2-	O		C ₂₄ H ₂₉ N ₅ O ₄ S
303545	2-MeO-Ph	H	Ac	-(CH2)2-	O		C ₂₄ H ₂₉ N ₅ O ₃ S
303546	2-MeO-Ph	H	H	-(CH2)2-	O		C ₂₂ H ₂₇ N ₅ O ₂ S
303547	2-MeO-Ph	H	1-Naph- -CH2CH2	-(CH2)2-	O	3HCl	C ₃₄ H ₃₇ N ₅ O ₂ S .3HCl

SOURCE – BASF.

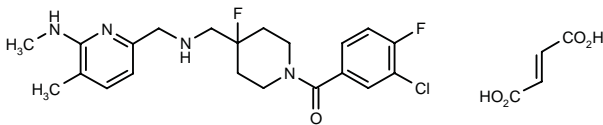
REFERENCES

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F-13714*

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SOURCE – Pierre Fabre (bioMérieux-Pierre Fabre).

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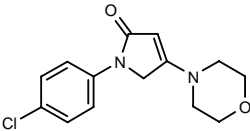
*Identified compound **265523** Drug Data Rep 1998, 020(09): 0753.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

302616

1-(4-Chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-pyrrol-2-one



C14 H15 Cl N2 O2; Mol wt: 278.7375

ACTION – Anticonvulsant and anxiolytic agent with a low liability to cause side effects. *In vivo*, compound protected rats against convulsions induced by maximal electroshock (ED₅₀ = 19 mg/kg p.o.) or pentylenetetrazol (ED₅₀ = 11 mg/kg p.o.), while displaying low neurotoxicity (NT₅₀ > 500 mg/kg p.o.). In addition, it exhibited anxiolytic effects in the Vogel conflict test in rats and in the elevated plus-maze model in mice at a dose of 10 mg/kg p.o. A representative compound from a series of 4-amino-1-aryl-1,5-dihydro-pyrrol-2-one derivatives.

SOURCE – Arzneimittelwerk Dresden.

REFERENCES

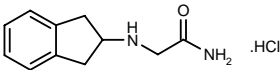
1. Arnold, T. et al. (Arzneimittelwerk Dresden GmbH) 4-Amino-1-aryl-1,5-dihydro-pyrrole-2-one with anti-convulsive and anxiolytic properties and a method for producing the same. DE 19944332, WO 0119793.

CHF-3381

300377

N-(2-Indanyl)glycinamide hydrochloride

2-(2,3-Dihydro-1H-inden-2-ylamino)acetamide hydrochloride



C11 H14 N2 O . HCl; Mol wt: 226.7055

ACTION – Antiepileptic agent, a low-affinity ligand for the NMDA receptor channel ($K_i = 8.8 \mu\text{M}$) proven to protect mice against NMDA-induced hind limb tonic extension ($\text{ED}_{50} = 10 \text{ mg/kg i.p.}$) and to antagonize behavioral effects and lethality induced by i.c.v. NMDA in mice ($\text{ED}_{50} = 57 \text{ mg/kg p.o.}$). Compound prevented maximal electroshock (MES)-induced seizures both in rats ($\text{ED}_{50} = 7.5$ and 21 mg/kg i.p. and p.o. , respectively) and mice ($\text{ED}_{50} = 24$ and 21 mg/kg i.p. and p.o. , respectively), was weaker against 4-aminopyridine- and bicuculline-induced tonic seizures in mice ($\text{ED}_{50} = 100 \text{ mg/kg i.p.}$ or p.o.), and was ineffective against pentylenetetrazol- and picrotoxin-induced clonic seizures. At anticonvulsant doses, compound only moderately reduced spontaneous locomotor activity in mice, did not affect motor performance in mice or rats and did not impair cognitive performance in mice. It exhibited a favorable pharmacokinetic profile with very rapid absorption and high brain levels.

SOURCE – Chiesi.

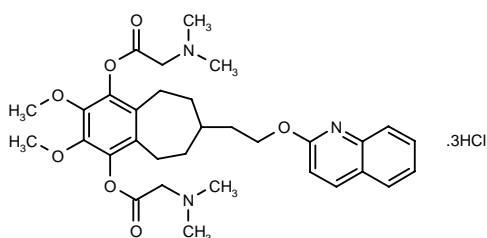
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1. Chiesi, P. et al. (Chiesi Farmaceutici SpA) *α -Amino acid amides, preparation thereof and the therapeutical use thereof*. EP 0951465, JP 2001506577, US 6114391, WO 9803472.
2. Villetti, G. et al. *Preclinical evaluation of CHF3381 as a novel antiepileptic agent*. Neuropharmacology 2001, 40(7): 866.
3. *R&D Pipeline*. Chiesi Group Web Site 2001, July 18.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

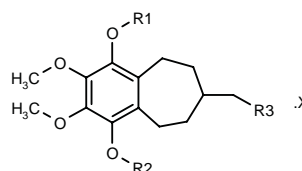
302111

2,3-Dimethoxy-7-[2-(2-quinolinylloxy)ethyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-1,4-diyl bis[2-(dimethylamino)acetate] trihydrochloride



C32 H41 N3 O7 . 3HCl; Mol wt: 689.0726

ACTION – Agent for the treatment of neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease with mitochondrial function-activating activity. *In vivo*, compound was shown to protect against anoxia-induced mortality in mice, prolonging survival time at 10-100 mg/kg p.o. Other bicyclic compounds include the following:



Compound	R1=R2	R3	X	Formula
302112	COCH2N(Me)2	4-Ph-1-Piz-CO	3HCl	C ₃₃ H ₄₆ N ₄ O ₇ ·3ClH
302115	H	4-Cl-PhOCH2		C ₂₁ H ₂₅ ClO ₅

SOURCE – Takeda.

REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *Agents for the activation of mitochondrial function*. JP 2001048784.

TREATMENT OF NEURODEGENERATIVE DISEASES

HA166-179

304802

L-Valyl-L-aspartyl-L-glutaminyl-L-tyrosyl-L-asparaginyl-L-asparaginyl-L-glutaminyl-L-asparaginyl-L-asparaginyl-L-phenylalanyl-L-valyl-L-histidyl-L-aspartyl-L-cysteine

C71 H100 N22 O26 S; Mol wt: 1709.7650

ACTION – Synthetic peptide corresponding to residues 166-179 of the hamster prion protein (PrP) sequence, able to strongly inhibit the formation of PrP ($\text{IC}_{50} = 10\text{-}15 \mu\text{M}$) and the protease-resistant isoforms of PrP, as well as to prevent the interaction between the two PrP isoforms (protease-resistant and -sensitive). Potentially useful for the treatment of transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease. Another related peptide is:

L-Glutamyl-L-threonyl-L-aspartyl-L-isoleucyl-L-lysyl-L-isoleucyl-L-methionyl-L-glutamyl-L-arginyl-L-valyl-L-valyl-L-glutamyl-L-glutaminyl-L-methionyl-L-cysteiny-L-threonyl-L-threonyl-L-glutaminyl-L-tyrosyl-L-glutaminyl-L-lysyl-L-glutamyl-L-seryl-L-glutamine

Ha200-223 [304803]: C121 H201 N33 O44 S3

SOURCES – National Institutes of Health, Bethesda, MD (US); Obihiro University of Agriculture and Veterinary Medicine, Obihiro (JP).

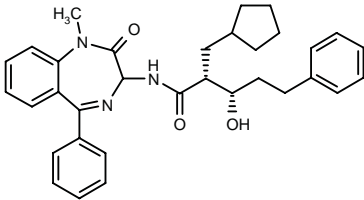
REFERENCES

1. Horiuchi, M. et al. *Inhibition of interactions and interconversions of prion protein isoforms by peptide fragments from the C-terminal folded domain*. J Biol Chem 2001, 276(18): 15489.

TREATMENT OF COGNITION
DISORDERS

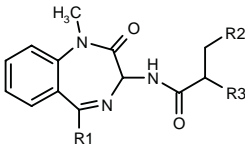
302770

2(*R*)-(Cyclopentylmethyl)-3(*S*)-hydroxy-*N*-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl)-5-phenylpentanamide



C33 H37 N3 O3; Mol wt: 523.6733

ACTION – An inhibitor of the production of β -amyloid peptide that acts by inhibiting γ -secretase, potentially useful for the treatment of neurological disorders related to β -amyloid production such as Alzheimer's disease and Down's syndrome. Other specifically claimed compounds from this series of hydroxyalkanoyl aminolactams include the following:



Compound	R1	R2	R3	Isomer	Formula
302771	Ph	i-Pr	cyclohexyl- -OCH2CH(OH)	2R,3S	C ₃₀ H ₃₉ N ₃ O ₄
302772	Ph	H	CH(OH)- (CH2)3Ph	2R,3S	C ₂₉ H ₃₁ N ₃ O ₃
302773	4-CF3-Ph	cyclopropyl	CH(OH)CH2- CH2CH=CH2	2R,3S	C ₂₈ H ₃₀ F ₃ N ₃ O ₃
302774	Ph	2-furyl	CH(OH)Bu	2R,3S,3'S	C ₂₈ H ₃₁ N ₃ O ₄
302775	Ph	Pr	CH(OH)Bu	2R,3S,3'S	C ₂₇ H ₃₅ N ₃ O ₃
302776	4-CF3-Ph	cyclopropyl	CH(OH)Bu	2S,3R	C ₂₈ H ₃₂ F ₃ N ₃ O ₃
302777	cycloheptyl	cyclopropyl	CH(OH)Bu	2R,3S	C ₂₈ H ₄₁ N ₃ O ₃
302778	4-CF3-Ph	cyclopropyl	COBu	2R,3S	C ₂₈ H ₃₀ F ₃ N ₃ O ₃

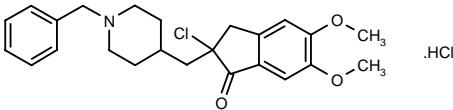
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Olson, R.E. et al. (DuPont Pharmaceuticals Co.) *Hydroxyalkanoyl aminolactams and related structures as inhibitors of Abeta protein production*. WO 0119797.

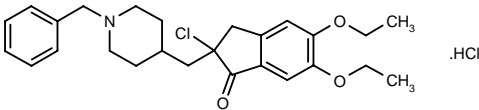
302925

2-(1-Benzylpiperidin-4-ylmethyl)-2-chloro-5,6-dimethoxy-indan-1-one hydrochloride



C24 H28 Cl N O3 . HCl; Mol wt: 450.4031

ACTION – Acetylcholinesterase inhibitor (IC₅₀ = 2.0 nM against enzyme from rat brain homogenates versus 6.7 nM for donepezil), potentially useful for the treatment of Alzheimer's disease, senile dementia, cerebrovascular dementia and attention deficit hyperactivity disorder. Another compound from this series of 4-substituted piperidine derivatives is:



302926: C26 H32 Cl N O3 . HCl

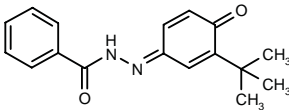
SOURCE – Eisai.

REFERENCES

1. Iimura, Y. and Kosasa, T. (Eisai Co., Ltd.) *4-Substd. piperidine derivs*. JP 2001139547, WO 0116105.

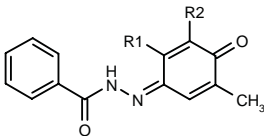
302982

N'-(3-*tert*-Butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-benzohydrazide



C17 H18 N2 O2; Mol wt: 282.3412

ACTION – Neurotrophic agent and nerve growth factor (NGF) potentiator proven to enhance the effects of NGF in promoting neurite outgrowth in rat pheochromocytoma PC12 cells at a concentration of 10 μ g/ml. Potentially useful for the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Other exemplified compounds from this series of hydrazide derivatives include the following:



Compound	R1	R2	Formula
302983	H	Me	C ₁₅ H ₁₄ N ₂ O ₂
302984	Me	H	C ₁₅ H ₁₄ N ₂ O ₂

SOURCE – Taisho.

REFERENCES

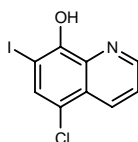
1. Mizoue, K. et al. (Taisho Pharmaceutical Co., Ltd.) *Hydrazide derivs.* JP 2001055369.

CLIOQUINOL

305111

5-Chloro-7-iodoquinolin-8-ol

PBT-1



C9 H5 Cl I N O; Mol wt: 305.4975

ACTION – Copper/zinc chelator able to cross the blood–brain barrier and to solubilize β -amyloid (A β) deposits in postmortem human Alzheimer's disease (AD) brain samples. In the APP2576 transgenic mouse model of AD, 9 weeks of oral treatment with compound attenuated and possibly reversed the accumulation of A β deposits in these animals; doses of 20 or 30 mg/kg/day produced 49-65% reductions in sedimentable A β in the brain, which was associated with a significant increase in soluble A β levels. Moreover, in 2 animals in the 20 mg/kg/day group no A β could be detected in brain pellet fractions and no neocortical or cortical amyloid pathology was seen. No signs of toxicity in terms of weight and survival were seen. A phase I clinical trial in patients with AD has been completed and no adverse effects were seen when clioquinol was administered with vitamin B12 supplementation to prevent the development of subacute myelo optic neuropathy, and a phase II trial is currently in progress.

SOURCES – Massachusetts General Hospital, Boston, MA (US); Prana Biotechnology.

REFERENCES

1. Bush, A.L. et al. (General Hospital Corporation) *Agents for use in the treatment of Alzheimer's disease.* WO 9945907.
2. Cherny, R.A. et al. *Treatment with a copper-zinc chelator markedly and rapidly inhibits β -amyloid accumulation in Alzheimer's disease transgenic mice.* Neuron 2001, 30: 665.
3. *Company Profile: Prana Biotechnology.* DailyDrugNews.com (Daily Essentials) 2001, July 11.
5. *Copper/zinc chelator may address underlying cause of Alzheimer's disease.* DailyDrugNews.com (Daily Essentials) 2001, June 26.
6. Parana Biotechnology Annual Report 2000.

DEXEFAROXAN

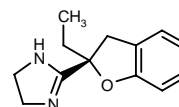
Prop INN

256934

(*R*)-(+)-2-(2-Ethyl-2,3-dihydrobenzofuran-2-yl)-4,5-dihydro-1*H*-imidazole

(*R*)-(+)-2-(2-Ethyl-2,3-dihydrobenzofuran-2-yl)-2-imidazoline

(+)-Efaroxan



C13 H16 N2 O; Mol wt: 216.2824

ACTION – Potent and selective α_2 -adrenoceptor antagonist proven to antagonize hypothermia induced by the selective central α_2 -adrenoceptor agonist guanabenz in mice (ED₅₀ = 0.05 and 0.11 mg/kg i.p. and p.o., respectively). Compound dose-dependently increased cortical release of noradrenaline and acetylcholine, and improved cognitive performance in young rats, ameliorated the age-related deficits in old rats and reversed the memory deficits induced by excitotoxic lesions of the nucleus basalis magnocellularis region in rats. Potentially useful for the treatment cognitive deficits occurring in disorders such as Alzheimer's disease.

SOURCES – Pierre Fabre (bioMérieux-Pierre Fabre); Reckitt & Colman.

REFERENCES

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2. Chapleo, C.B. et al. (Reckitt & Colman Pharmaceuticals) *Imidazoline derivs.* WO 9205171.
3. Imbert, T. and Mayer, P. (Pierre Fabre Médicament) *Method for preparing an optically pure benzofuran carboxylic acid and use thereof for preparing efaroxan.* FR 2733983, US 5880296, WO 9635682.
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5. Bauer, S. et al. *Anti-apoptotic effect of the α_2 -adrenoceptor antagonist dexefaroxan in the olfactory bulb of adult rat brain in vivo.* Soc Neurosci Abst 2000, 26(Part 2): Abst 514.17.
6. Chan, S.L.F. et al. *Stimulation of insulin secretion by the imidazoline α_2 -adrenoceptor antagonist efaroxan is mediated by a novel, stereoselective, binding site.* Eur J Pharmacol 1993, 230(3): 375.
7. Chopin, P. et al. *Effects of α_2 -adrenoceptor agonists and antagonists on circling behavior in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal pathway.* J Pharmacol Exp Ther 1999, 288(2): 798.
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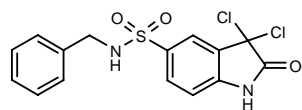
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SB-263831

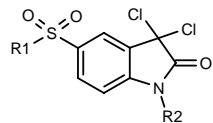
302960

N-Benzyl-3,3-dichloro-2-oxoindoline-5-sulfonamide



C15 H12 Cl2 N2 O3 S; Mol wt: 371.2428

ACTION – An inhibitor of caspases, particularly caspase 3 and caspase 7, potentially useful for blocking excess or inappropriate apoptosis, for example in Alzheimer’s disease, viral infections, ischemia, infarction or reperfusion injury, bone disorders, osteoarthritis or hepatocellular degeneration. Within this series of 3,3-dichloro-2-oxoindoline-5-sulfonamide derivatives, the following compounds are also included:



Compound	R1	R2	Formula
SB-265241 [302962]	2-furyl-CH2NH	H	C ₁₃ H ₁₀ Cl ₂ N ₂ O ₄ S
SB-265248 [302964]	2-indanyl-NH	H	C ₁₇ H ₁₄ Cl ₂ N ₂ O ₃ S
SB-265551 [302966]	3-[AcN(Me)]-1-pyrrolidinyl	H	C ₁₅ H ₁₇ Cl ₂ N ₃ O ₄ S
SB-265598 [302967]	1-pyrrolidinyl	H	C ₁₂ H ₁₂ Cl ₂ N ₂ O ₃ S
SB-265603 [302968]	4-morpholinyl	H	C ₁₂ H ₁₂ Cl ₂ N ₂ O ₄ S
SB-265608 [302969]	3-OH-1-pyrrolidinyl	H	C ₁₂ H ₁₂ Cl ₂ N ₂ O ₄ S
SB-264733 [302970]	2-(HOCH2CH2)-1-Pip	H	C ₁₅ H ₁₈ Cl ₂ N ₂ O ₄ S
SB-263921 [302971]	1-Pip	Me	C ₁₄ H ₁₆ Cl ₂ N ₂ O ₃ S

SOURCE – GlaxoSmithKline.

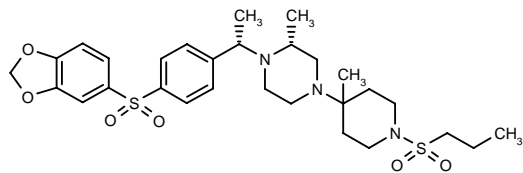
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SCH-72788

304738

1-[1(S)-[4-(1,3-Benzodioxol-5-ylsulfonyl)phenyl]ethyl]-2(R)-methyl-4-[4-methyl-1-(propylsulfonyl)piperidin-4-yl]piperazine



C29 H41 N3 O6 S2; Mol wt: 577.7631

ACTION – Potent and selective muscarinic M₂ antagonist (K_i = 0.5, 3, 42, 23 and 35 nM for M₂, M₄, M₁, M₃ and M₅ receptors, respectively) with functional antagonist activity in CHO cells expressing M₃ receptors, where it competitively antagonized the oxotremorine-induced inhibition of ATP production (K_b = 0.8 nM). *In vivo*, following either i.v. or oral administration, it increased acetylcholine release from the striatum of conscious rats, and it significantly improved cognitive performance in a passive avoidance paradigm in rats when given at doses of 0.03-0.3 mg/kg p.o. Potentially useful for the treatment of the cognitive disorders including Alzheimer’s disease.

SOURCE – Schering-Plough.

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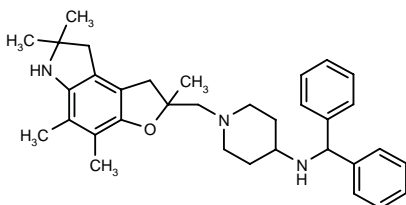
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TREATMENT OF CEREBROVASCULAR DISEASES

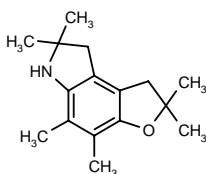
302182

N-(Diphenylmethyl)-1-(2,4,5,7,7-pentamethyl-2,6,7,8-tetrahydro-1*H*-furo[3,2-*e*]indol-2-ylmethyl)piperidin-4-amine



C34 H43 N3 O; Mol wt: 509.7337

ACTION – Agent with excellent inhibitory activity against lipid peroxidation ($IC_{50} = 0.057 \mu M$ in rat cortex homogenates) and potential in the treatment of a broad range of disorders including cerebral ischemic disorders, head and spinal cord injury, neurodegenerative disorders, psychoses, depression, schizophrenia, chronic pain, migraine, ischemic cardiopathy, arteriosclerosis, restenosis following PTCA and lower urinary tract disorders. Another compound from this series of tricyclic dihydrobenzofuran derivatives is:



302183: C16 H23 N O

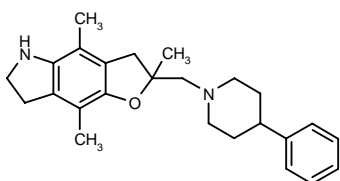
SOURCE – Takeda.

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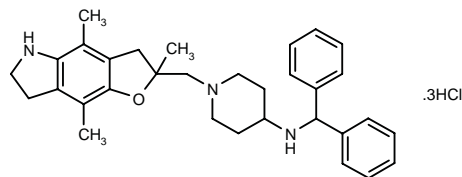
302184

2,4,8-Trimethyl-2-(4-phenylpiperidin-1-ylmethyl)-3,5,6,7-tetrahydro-2*H*-furo[2,3-*f*]indole



C25 H32 N2 O; Mol wt: 376.5408

ACTION – Agent with excellent inhibitory activity against lipid peroxidation ($IC_{50} = 0.067 \mu M$ in rat cortex homogenates) and potential in the treatment of a broad range of disorders including cerebral ischemic disorders, head and spinal cord injury, neurodegenerative disorders, psychoses, depression, schizophrenia, chronic pain, migraine, ischemic cardiopathy, arteriosclerosis, restenosis following PTCA and lower urinary tract disorders. Another compound from this series of tricyclic dihydrobenzofuran derivatives is:



302185: C32 H39 N3 O . 3HCl

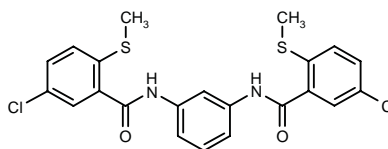
SOURCE – Takeda.

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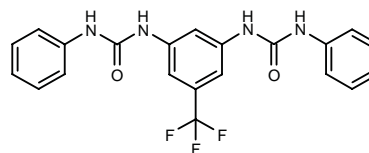
302358

N,N'-(1,3-Phenylene)bis[5-chloro-2-(methylsulfanyl)-benzamide]



C22 H18 Cl2 N2 O2 S2; Mol wt: 477.4342

ACTION – Neuroprotective agent that selectively binds to cyclophilin proteins, as demonstrated by inhibition of cyclophilin romatase activity at $10 \mu M$ or below. It promotes neuronal cell growth, regenerates damaged neurons and protects against neuronal damage. Another exemplified nonpeptide compound is:



302360: C21 H17 F3 N4 O2

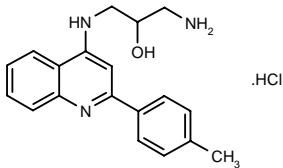
SOURCE – Guilford.

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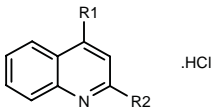
302996

1-Amino-3-[2-(4-methylphenyl)quinolin-4-ylamino]propan-2-ol hydrochloride



C19 H21 N3 O . HCl; Mol wt: 343.8558

ACTION – NMDA receptor subtype-selective blocker giving an IC₅₀ value of 0.02 μM against [³H]-Ro-25-6981 binding in rat brain membrane homogenates. Potentially useful for the treatment of CNS disorders, particularly acute forms of neurodegeneration such as those caused by stroke or brain trauma, chronic neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis and neurodegeneration associated with bacterial or viral infections. Other specifically claimed compounds from this series of quinolin-4-yl derivatives include the following:



Compound	R1	R2	Formula
302997	NHCH2CH(OH)CH2NH2	1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₁ H ₂₄ N ₄ O.HCl
302998	NHCH2CH2OH	5,6,7,8-tetrahydro-2-Naph	C ₂₁ H ₂₂ N ₂ O.HCl
302999	NHCH2CH(OH)-CH2NHMe	4-MeO-Ph	C ₂₀ H ₂₃ N ₃ O ₂ .HCl
303000	NHCH2CH(OH)CH2OH	2,3-dihydro-5-benzofuryl	C ₂₀ H ₂₀ N ₂ O ₃ .HCl
303001	CH2NHCH2CH2OH	4-MeO-Ph	C ₁₉ H ₂₀ N ₂ O ₂ .HCl

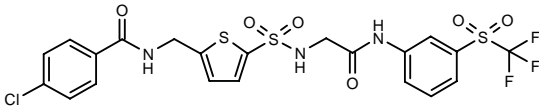
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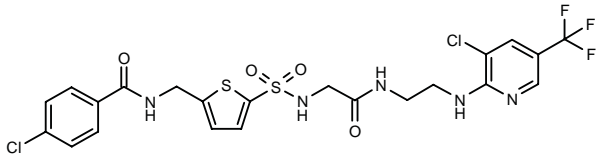
303271

4-Chloro-N-[5-[N-[2-oxo-2-[3-(trifluoromethylsulfonyl)phenylamino]ethyl]sulfamoyl]thien-2-ylmethyl]benzamide



C21 H17 Cl F3 N3 O6 S3; Mol wt: 596.0253

ACTION – A selective inhibitor of Jun kinases JNK2 and JNK3, as demonstrated *in vitro* by IC₅₀ values of 1.3 and 0.64 μM against recombinant kinases, respectively, compared to IC₅₀ values > 30 μM against p38 MAP kinase and ERK2. Potentially useful for the treatment of neuronal disorders such as epilepsy, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, spinal cord injury and head trauma, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock and transplant rejection, cancer and cardiovascular disorders such as myocardial infarction, myocardial reperfusion injury, atherosclerosis and stroke. Another compound from this series of sulfonyl amino acid derivatives is:



303272: C22 H20 Cl2 F3 N5 O4 S2

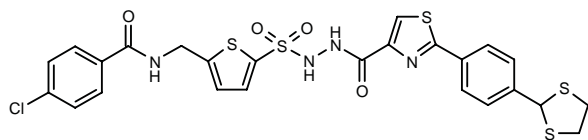
SOURCE – Applied Research Systems.

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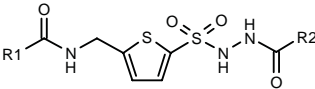
303273

4-Chloro-N-[5-[2-[2-[4-(1,3-dithiolan-2-yl)phenyl]thiazol-4-ylcarbonyl]hydrazinosulfonyl]thien-2-ylmethyl]benzamide

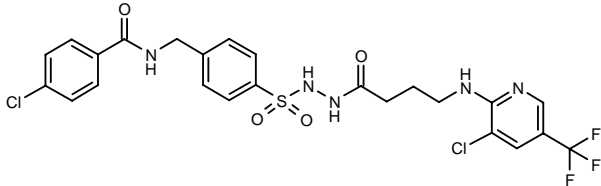


C25 H21 Cl N4 O4 S5; Mol wt: 637.2479

ACTION – A selective inhibitor of Jun kinases JNK2 and JNK3, as demonstrated *in vitro* by IC₅₀ values of 0.37 and 0.21 μM against recombinant kinases, respectively, compared to IC₅₀ values > 30 μM against p38 MAP kinase and ERK2. Compound was further shown to inhibit PMA/ionomycin-stimulated IL-2 production in Jurkat cells (> 30% inhibition at 3 μM), as well as c-Jun expression in a luciferase reporter gene assay in Hlr c-Jun HeLa cells (> 20% inhibition at 10 μM). Potentially useful for the treatment of neuronal disorders such as epilepsy, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, spinal cord injury and head trauma, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock and transplant rejection, cancer and cardiovascular disorders such as myocardial infarction, myocardial reperfusion injury, atherosclerosis and stroke. Other exemplified compounds from this series of sulfonyl hydrazide derivatives include the following:



Compound	R1	R2	Formula
303274	4-Cl-Ph	2-(2-Cl-PhOCH2)-4-thiazolyl	C ₂₃ H ₁₈ Cl ₂ N ₄ O ₅ S ₃
303275	2-OH-Ph	3-Cl-5-CF ₃ -2-Pyr-NH(CH ₂) ₃	C ₂₂ H ₂₁ ClF ₃ N ₅ O ₅ S ₂
303276	2-oxo- -1,2-dihydro-3-Pyr	3-Cl-5-CF ₃ -2-Pyr-NH(CH ₂) ₃	C ₂₁ H ₂₀ ClF ₃ N ₆ O ₅ S ₂



303277: C₂₄ H₂₂ Cl₂ F₃ N₅ O₄ S

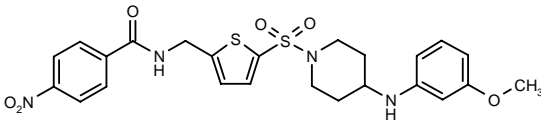
SOURCE – Applied Research Systems.

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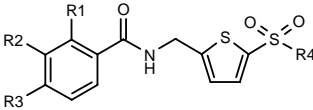
303278

N-[5-[4-(3-Methoxyphenylamino)piperidin-1-ylsulfonyl]-thien-2-ylmethyl]-4-nitrobenzamide



C₂₄ H₂₆ N₄ O₆ S₂; Mol wt: 530.6234

ACTION – A selective inhibitor of Jun kinases JNK2 and JNK3, as demonstrated *in vitro* by IC₅₀ values of 0.22 and 0.17 μM against recombinant kinases, respectively, compared to IC₅₀ values > 30 μM against p38 MAP kinase and ERK2. Compound was further shown to inhibit PMA/ionomycin-stimulated IL-2 production in Jurkat cells (> 30% inhibition at 3 μM), as well as c-Jun expression in a luciferase reporter gene assay in Hlr c-Jun HeLa cells (> 30% inhibition at 10 μM). Potentially useful for the treatment of neuronal disorders such as epilepsy, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, spinal cord injury and head trauma, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock and transplant rejection, cancer and cardiovascular disorders such as myocardial infarction, myocardial reperfusion injury, atherosclerosis and stroke. Other exemplified compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
303279	H	H	Cl	4-[2,4-(F)2-PhCO]-1-Pip	C ₂₄ H ₂₁ ClF ₂ N ₂ O ₄ S ₂
303282	H	H	Cl	4-(PhCH ₂ CO)-perhydro- -1,4-diazepin-1-yl	C ₂₅ H ₂₆ ClN ₃ O ₄ S ₂
303283	H	H	Cl	4-(PhNH)-1-Pip	C ₂₃ H ₂₄ ClN ₃ O ₃ S ₂
303284	H	H	Cl	4-(1,2,3-benzo- triazol-1-yl)-1-Pip	C ₂₃ H ₂₂ ClN ₅ O ₃ S ₂
303285	H	H	Cl	4-(1-benzimidazolyl)-1-Pip	C ₂₄ H ₂₃ ClN ₄ O ₃ S ₂
303286	H	H	Cl	4-(3-Pr-PhNH)-4-Pip	C ₂₆ H ₃₀ ClN ₃ O ₃ S ₂
303287	H	H	Cl	4-(4-Cl-PhNH)-1-Pip	C ₂₃ H ₂₃ Cl ₂ N ₃ O ₃ S ₂
303288	H	H	Cl	4-[3-(HOCH ₂ CH ₂ SO ₂)- -PhNH]-1-Pip	C ₂₅ H ₂₈ ClN ₃ O ₆ S ₃
303289	H	H	Cl	4-[3-(NH ₂ SO ₂)-PhNH]-1-Pip	C ₂₃ H ₂₅ ClN ₄ O ₅ S ₃
303290	H	H	Cl	4-(1-Naph-CO)-1-Piz	C ₂₇ H ₂₄ ClN ₃ O ₄ S ₂
303291	H	H	NO ₂	4-[3-(CO ₂ Me)-PhNH]-1-Pip	C ₂₅ H ₂₆ N ₄ O ₇ S ₂
303292	OH	H	H	4-(1,2,3-benzo- triazol-1-yl)-1-Pip	C ₂₃ H ₂₃ N ₅ O ₄ S ₂
303293	H	OMe	H	4-(2-NO ₂ -PhNH)-1-Pip	C ₂₄ H ₂₆ N ₄ O ₆ S ₂

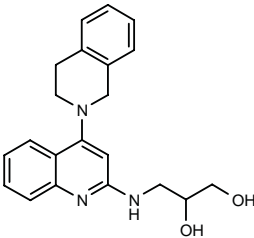
SOURCE – Applied Research Systems.

REFERENCES

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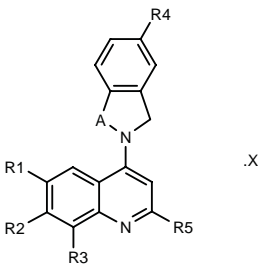
303405

3-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)quinolin-2-yl-amino]propane-1,2-diol



C₂₁ H₂₃ N₃ O₂; Mol wt: 349.4317

ACTION – An NMDA receptor antagonist that is potentially useful for the treatment of acute forms of neuro-degeneration caused by stroke or brain trauma, and chronic neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease and amyotrophic lateral sclerosis. Other exemplified quinolines are:



Compound	R1	R2	R3	R4	R5	A	X	Formula
303406	H	H	H	H	(S)-NHCH2-CH(OH)Me	-(CH2)2-		C ₂₁ H ₂₃ N ₃ O
303407	H	H	H	H	NH2	-(CH2)2-		C ₁₈ H ₁₇ N ₃
303408	H	H	H	H	H	-(CH2)2-		C ₁₈ H ₁₆ N ₂
303409	H	H	H	Cl	H	-CH2-		C ₁₇ H ₁₃ ClN ₂
303410	H	H	H	H	H	-CH2-		C ₁₇ H ₁₄ N ₂
303411	H	H	H	H	NHCH2CH2OH	-(CH2)2-	HCl	C ₂₀ H ₂₁ N ₃ O.HCl
303412	H	H	H	H	3(R)-OH-1-pyrrolidinyl	-(CH2)2-	HCl	C ₂₂ H ₂₃ N ₃ O.HCl
303413	H	H	H	H	2(R)-(OHCH2)-1-pyrrolidinyl	-(CH2)2-		C ₂₃ H ₂₅ N ₃ O
303414	H	Me	H	H	H	-(CH2)2-	HCl	C ₁₉ H ₁₈ N ₂ .HCl
303416	H	Cl	H	H	H	-(CH2)2-	HCl	C ₁₈ H ₁₄ ClN ₂ .HCl
303417	H	H	F	H	H	-(CH2)2-	HCl	C ₁₈ H ₁₅ FN ₂ .HCl
303418	F	H	H	H	H	-(CH2)2-	HCl	C ₁₈ H ₁₅ FN ₂ .HCl

SOURCE – Roche.

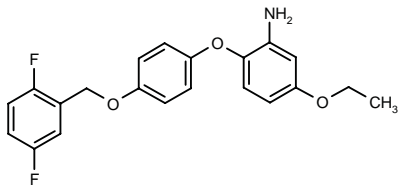
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SEA-0400*

277293

2-[4-(2,5-Difluorobenzyloxy)phenoxy]-5-ethoxyphenyl-amine



C21 H19 F2 N O3; Mol wt: 371.3811

ACTION – Potent and selective inhibitor of the Na⁺/Ca²⁺ exchanger (NCX) with IC₅₀ values of 33, 5 and 8.3 nM, respectively, for inhibition of Na⁺-dependent Ca²⁺ uptake in cultured rat neurons, astrocytes and microglia. Compound did not affect store-operated Ca²⁺ entry up to 3 μM and had negligible activity against Ca²⁺, Na⁺, and K⁺ channels, the noradrenaline transporter, a range of receptors, enzymes and other ion transporters. In cultured astrocytes, compound attenuated Ca²⁺ paradox-like injury, DNA ladder formation and nuclear condensation. *In vivo* in a model of cerebral ischemia induced by transient middle cerebral artery occlusion in rats, compound at a dose of 3 mg/kg i.v. by bolus followed by 3 mg/kg/h for 2 h, significantly reduced cortical and striatal infarct volume. In a dog coronary occlusion model, compound given 1 min before reperfusion at a dose of 1 mg/kg i.v. improved recovery of myocardial infarct volume.

SOURCE – Taisho.

REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Na⁺/Ca²⁺ exchange inhibitors*. JP 2000355537.

2. Ota, T. et al. (Taisho Pharmaceutical Co., Ltd.) *2-Phenoxyaniline derivs*. EP 1031556, JP 1999193263, WO 9920598.

3. Iwamoto, T. *Structure, function and pathophysiology of Na⁺/Ca²⁺ exchanger*. Jpn J Circ Res 2001, 24(3): 101.

4. Matsuda, T. et al. *SEA0400, a novel and selective inhibitor of the Na⁺-Ca²⁺ exchanger, attenuates reperfusion injury in the in vitro and in vivo cerebral ischemic models*. J Pharmacol Exp Ther 2001, 298(1): 249.

5. Takahashi, T. et al. *Na⁺/Ca²⁺ exchange may play an important role in ischemia-reperfusion injury in in vivo heart and brain*. J Am Coll Cardiol 2001, 37(2, Suppl. A): 324A.

*Identified compound **277293** (see **277290**) Drug Data Rep 1999, 021(07): 0603.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

SYNTHETIC NEUTROPHIL INHIBITOR
PEPTIDE

304162

N^α-Acetyl-L-arginyl-L-glutamyl-glycyl-L-seryl-L-tyrosyl-L-phenylalanyl-L-phenylalanyl-glycyl-L-aspartyl-L-asparaginy-L-alaninamide

SNIP

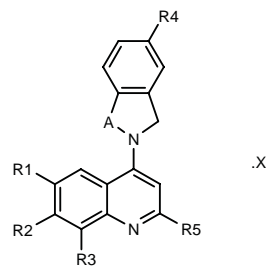
C58 H78 N16 O19; Mol wt: 1303.3470

ACTION – Synthetic neutrophil inhibitor peptide proven to inhibit polymorphonuclear neutrophil (PMN) chemotaxis induced by IL-8 *in vitro* (IC₅₀ < 1 μM), increase apoptosis in PMNs and attenuate the inflammatory nasal response to inhaled IL-8 in healthy human volunteers. In addition, the peptide appears to specifically bind PMNs via the CR3 integrin. Potentially useful for the treatment of nasal inflammation including allergic rhinitis.

SOURCES – University of Alabama, Birmingham, AL (US); Veterans Administration Medical Center, Hartford, VT (US).

REFERENCES

1. Cooper, J.A.D. Jr. et al. *Attenuation of interleukin 8-induced nasal inflammation by an inhibitor peptide*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): 1198.



Compound	R1	R2	R3	R4	R5	A	X	Formula
303406	H	H	H	H	(S)-NHCH2-CH(OH)Me	-(CH2)2-		C ₂₁ H ₂₃ N ₃ O
303407	H	H	H	H	NH2	-(CH2)2-		C ₁₈ H ₁₇ N ₃
303408	H	H	H	H	H	-(CH2)2-		C ₁₈ H ₁₆ N ₂
303409	H	H	H	Cl	H	-CH2-		C ₁₇ H ₁₃ ClN ₂
303410	H	H	H	H	H	-CH2-		C ₁₇ H ₁₄ N ₂
303411	H	H	H	H	NHCH2CH2OH	-(CH2)2-	HCl	C ₂₀ H ₂₁ N ₃ O.HCl
303412	H	H	H	H	3(R)-OH-1-pyrrolidinyl	-(CH2)2-	HCl	C ₂₂ H ₂₃ N ₃ O.HCl
303413	H	H	H	H	2(R)-(OHCH2)-1-pyrrolidinyl	-(CH2)2-		C ₂₃ H ₂₅ N ₃ O
303414	H	Me	H	H	H	-(CH2)2-	HCl	C ₁₉ H ₁₈ N ₂ .HCl
303416	H	Cl	H	H	H	-(CH2)2-	HCl	C ₁₈ H ₁₄ ClN ₂ .HCl
303417	H	H	F	H	H	-(CH2)2-	HCl	C ₁₈ H ₁₅ FN ₂ .HCl
303418	F	H	H	H	H	-(CH2)2-	HCl	C ₁₈ H ₁₅ FN ₂ .HCl

SOURCE – Roche.

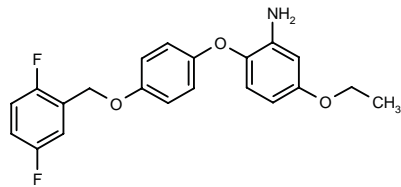
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1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *Quinolin-4-yl derivs. and their use as NMDA-receptor subtype blockers*. EP 1090917, JP 2001114777.

SEA-0400*

277293

2-[4-(2,5-Difluorobenzyloxy)phenoxy]-5-ethoxyphenyl-amine



C21 H19 F2 N O3; Mol wt: 371.3811

ACTION – Potent and selective inhibitor of the Na⁺/Ca²⁺ exchanger (NCX) with IC₅₀ values of 33, 5 and 8.3 nM, respectively, for inhibition of Na⁺-dependent Ca²⁺ uptake in cultured rat neurons, astrocytes and microglia. Compound did not affect store-operated Ca²⁺ entry up to 3 μM and had negligible activity against Ca²⁺, Na⁺, and K⁺ channels, the noradrenaline transporter, a range of receptors, enzymes and other ion transporters. In cultured astrocytes, compound attenuated Ca²⁺ paradox-like injury, DNA ladder formation and nuclear condensation. *In vivo* in a model of cerebral ischemia induced by transient middle cerebral artery occlusion in rats, compound at a dose of 3 mg/kg i.v. by bolus followed by 3 mg/kg/h for 2 h, significantly reduced cortical and striatal infarct volume. In a dog coronary occlusion model, compound given 1 min before reperfusion at a dose of 1 mg/kg i.v. improved recovery of myocardial infarct volume.

SOURCE – Taisho.

REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Na⁺/Ca²⁺ exchange inhibitors*. JP 2000355537.

2. Ota, T. et al. (Taisho Pharmaceutical Co., Ltd.) *2-Phenoxyaniline derivs*. EP 1031556, JP 1999193263, WO 9920598.

3. Iwamoto, T. *Structure, function and pathophysiology of Na⁺/Ca²⁺ exchanger*. Jpn J Circ Res 2001, 24(3): 101.

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*Identified compound **277293** (see **277290**) Drug Data Rep 1999, 021(07): 0603.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

SYNTHETIC NEUTROPHIL INHIBITOR PEPTIDE

304162

N^α-Acetyl-L-arginyl-L-glutamyl-glycyl-L-seryl-L-tyrosyl-L-phenylalanyl-L-phenylalanyl-glycyl-L-aspartyl-L-asparaginyL-L-alaninamide

SNIP

C58 H78 N16 O19; Mol wt: 1303.3470

ACTION – Synthetic neutrophil inhibitor peptide proven to inhibit polymorphonuclear neutrophil (PMN) chemotaxis induced by IL-8 *in vitro* (IC₅₀ < 1 μM), increase apoptosis in PMNs and attenuate the inflammatory nasal response to inhaled IL-8 in healthy human volunteers. In addition, the peptide appears to specifically bind PMNs via the CR3 integrin. Potentially useful for the treatment of nasal inflammation including allergic rhinitis.

SOURCES – University of Alabama, Birmingham, AL (US); Veterans Administration Medical Center, Hartford, VT (US).

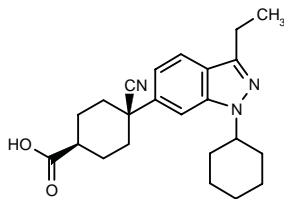
REFERENCES

1. Cooper, J.A.D. Jr. et al. *Attenuation of interleukin 8-induced nasal inflammation by an inhibitor peptide*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): 1198.

ASTHMA THERAPY

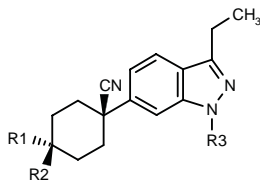
302373

cis-4-Cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid

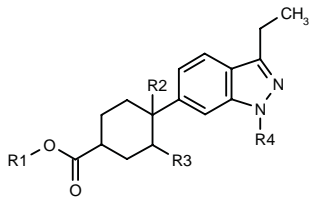


C23 H29 N3 O2; Mol wt: 379.5011

ACTION – An inhibitor of phosphodiesterase type 4 (PDE 4) and TNF production, potentially useful in the treatment of a broad range of disorders including asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis, AIDS and septic shock. Other specifically claimed compounds from this series of substituted indazole derivatives include the following:



Compound	R1	R2	R3	Formula
302379	H	CO2H	cyclopentyl	C ₂₂ H ₂₇ N ₃ O ₂
302380	CO2Me	H	cyclohexyl	C ₂₄ H ₃₁ N ₃ O ₂
302381	H	CH2OH	cyclohexyl	C ₂₃ H ₃₁ N ₃ O
302382	H	OH	cyclopentyl	C ₂₁ H ₂₇ N ₃ O
302383	H	CO2H	cyclobutyl	C ₂₁ H ₂₅ N ₃ O ₂
302576	H	CO2H	4-F-Ph	C ₂₃ H ₂₂ FN ₃ O ₂



Compound	R1	R2	R3	R4	Formula
302384	Et	bond		4-F-Ph	C ₂₄ H ₂₅ FN ₂ O ₂
302385	H	OH	H	cyclohexyl	C ₂₂ H ₃₀ N ₂ O ₃

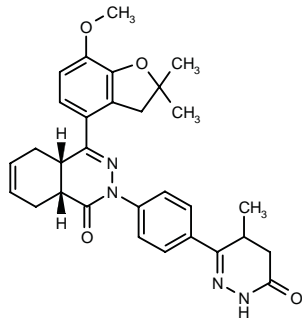
SOURCE – Pfizer.

REFERENCES

1. Marfat, A. (Pfizer Inc.) *Substd. indazole derivs. and related cpds.* US 6211222.

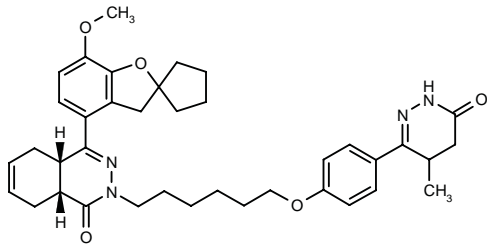
302617

cis-4-(7-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-4-yl)-2-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]-1,2,4a,5,8,8a-hexahydrophthalazin-1-one



C30 H32 N4 O4; Mol wt: 512.6068

ACTION – A phosphodiesterase type 4 (PDE4) inhibitor that exhibited respective –log IC₅₀ values of 10.35 and 7.46 when tested for inhibition of PDE4 and PDE3 isozymes. Potentially useful for the treatment of airways disorders, particularly those of an inflammatory nature. Another exemplified phthalazinone derivative is:



302619: C38 H46 N4 O5

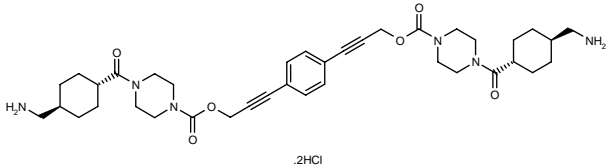
SOURCE – Byk Gulden.

REFERENCES

1. Ulrich, W.-R. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Phthalazinone derivs. as PD3/4 inhibitors.* WO 0119818.

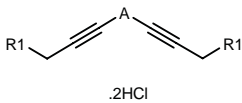
302681

3,3'-(1,4-Phenylene)bis(2-propyn-1-ol) diester with 4-[*trans*-4-(aminomethyl)cyclohexylcarbonyl]piperazine-1-carboxylic acid dihydrochloride



C38 H52 N6 O6 . 2HCl; Mol wt: 761.7866

ACTION – Human mast cell tryptase inhibitor (K_{iapp} = 0.003 μM), with potential for the treatment of airways disorders such as asthma, chronic obstructive pulmonary disease and bronchitis, as well as interstitial lung disorders, allergic rhinitis, arthritis, multiple sclerosis, psoriasis and inflammatory bowel disease. Other exemplified compounds from this series of bis-alkynyl derivatives include the following:



Compound	R1	A	Formula
302682	4-[4-(NH ₂ CH ₂)-PhCH ₂ NHCO]- -1-PiZ-COO	1,3-Ph	C ₄₀ H ₄₈ Cl ₂ N ₈ O ₆
302683	4-[4-(NH ₂ CH ₂)-PhCH ₂ NHCO]- -1-PiZ-COO	1,2-Ph	C ₄₀ H ₄₈ Cl ₂ N ₈ O ₆
302684	4-(NH ₂ CH ₂)-PhCH ₂ NHCOO	1,3-Ph	C ₃₀ H ₃₂ Cl ₂ N ₄ O ₄
302685	3-(NH ₂ CH ₂)-PhCH ₂ NHCOO	furyl-2,5-diyl	C ₂₈ H ₃₀ Cl ₂ N ₄ O ₅
302686	4-(NH ₂ CH ₂)-PhCH ₂ NHCOCH ₂ O	-1,4-Ph-	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₄
302687	4-(NH ₂ CH ₂)-PhCH ₂ NHCOCH ₂ O	1,3-Ph	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₄
302688	4-(NH ₂ CH ₂)-PhCH ₂ CH ₂ CONH	-1,4-Ph-	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₂

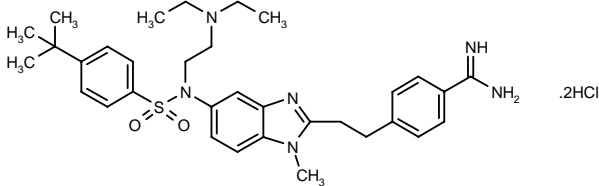
SOURCE – Byk Gulden.

REFERENCES

1. Bär, T. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Tryptase inhibitors*. WO 0119809.

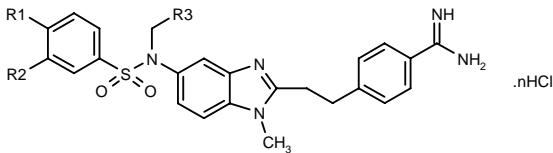
303316

4-[2-[5-[*N*-(4-*tert*-Butylphenylsulfonyl)-*N*-[2-(diethylamino)ethyl]amino]-1-methyl-1-*H*-benzimidazol-2-yl]ethyl]-benzamidinium dihydrochloride



C33 H44 N6 O2 S . 2HCl; Mol wt: 661.7384

ACTION – Agent for the treatment or prevention of inflammatory and allergic disorders such as asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, ulcerative colitis, Crohn's disease, anaphylactic shock, septic shock, adult respiratory distress syndrome and arthritis, as well as fibroses, lupus erythematosus, scleroderma, arteriosclerosis, psoriasis and cancer, an inhibitor of tryptase (IC_{50} = 0.0041 μ M against recombinant human β -tryptase). Other exemplified compounds from this series of aryl-sulfonamide substituted benzimidazole derivatives include the following:



Compound	R1	R2	R3	n	Formula
303317	CO ₂ Et	H	CH ₂ N(Et)2	1	C ₃₂ H ₄₀ N ₆ O ₄ S.HCl
303318	H	PhC(Me) ₂	CH ₂ N(Et)2	2	C ₃₈ H ₄₆ N ₆ O ₂ S.2HCl
303319	t-Bu	H	Ph	2	C ₃₄ H ₃₅ N ₆ O ₂ S.2HCl

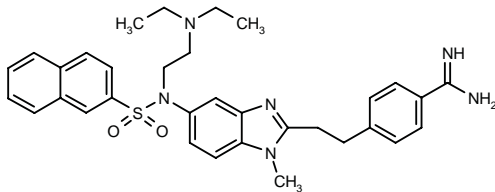
SOURCE – Bayer.

REFERENCES

1. Anderskewitz, R. et al. (Boehringer Ingelheim Pharma KG) *Aryl-sulfonamide subst. benzimidazol derivs. and use of said as tryptase inhibitors*. DE 19945810, WO 0123359.

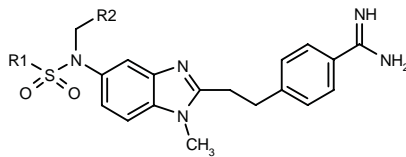
303320

4-[2-[5-[*N*-[2-(Diethylamino)ethyl]-*N*-(2-naphthylsulfonyl)-amino]-1-methyl-1*H*-benzimidazol-2-yl]ethyl]benzamidine



C33 H38 N6 O2 S; Mol wt: 582.7692

ACTION – Agent for the treatment or prevention of inflammatory and allergic disorders such as asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, ulcerative colitis, Crohn's disease, anaphylactic shock, septic shock, adult respiratory distress syndrome and arthritis, as well as fibroses, lupus erythematosus, scleroderma, arteriosclerosis, psoriasis and cancer, an inhibitor of tryptase ($IC_{50} = 0.0066 \mu M$ against recombinant human β -tryptase). Other exemplified compounds from this series of aryl-sulfonamide substituted benzimidazole derivatives include the following:



Compound	R1	R2	Formula
303321	1-Naph	CH ₂ N(Et) ₂	C ₃₃ H ₃₈ N ₆ O ₂ S
303322	3-benzothienyl	CH ₂ N(Et) ₂	C ₃₁ H ₃₆ N ₆ O ₂ S ₂
303323	2-Naph	2-Pyr	C ₃₃ H ₃₀ N ₆ O ₂ S
303324	2-Naph	3-Pyr	C ₃₃ H ₃₀ N ₆ O ₂ S
303325	8-quinolyl	CH ₂ N(Et) ₂	C ₃₂ H ₃₇ N ₇ O ₂ S
303326	Ph	(CH ₂) ₃ N(Me) ₂	C ₂₉ H ₃₆ N ₆ O ₂ S
303327	Ph	4-Me-1,4-diazepin-1-yl-CO	C ₃₁ H ₃₇ N ₇ O ₃ S

SOURCE – Boehringer Ingelheim.

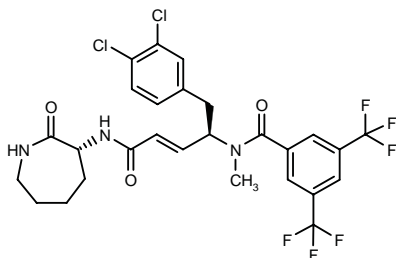
REFERENCES

1. Anderskewitz, R. et al. (Boehringer Ingelheim Pharma KG) *Aryl sulfonamide-subst. benzimidazol derivs. thereof as tryptase inhibitors*. DE 19945787, WO 0123360.

DNK-333A***264027**

5-(3,4-Dichlorophenyl)-4(*R*)-[*N*-methyl-3,5-bis(trifluoromethyl)benzamido]-*N*-[2-oxoperhydroazepin-3(*R*)-yl]-2(*E*)-pentenamide

N-[1(*R*)-(3,4-Dichlorobenzyl)-4-[hexahydro-2-oxo-1*H*-azepin-3(*R*)-ylamino]-4-oxo-2(*E*)-butenyl]-*N*-methyl-3,5-bis(trifluoromethyl)benzamide



C27 H25 Cl2 F6 N3 O3; Mol wt: 624.4065

ACTION – Dual tachykinin NK₁/NK₂ receptor antagonist with high affinity and selectivity for human NK₁ and NK₂ over NK₃ receptors (pK_i = 7.9, 8.02 and 6.87, respectively), proven to antagonize the bronchoconstriction induced by selective NK₁ and NK₂ agonists in guinea pig trachea (pK_B = 7.93 and 7.27, respectively). Compound antagonized the bronchoconstrictor response to an inhaled NK₂ agonist in monkeys (ED₅₀ = 1 mg/kg p.o.), the airways hyperresponsiveness to histamine or bombesin in actively sensitized guinea pigs (1-3 mg/kg p.o. 2 h prior to challenge), the nasal extravasation induced by substance P or capsaicin in guinea pigs (ED₅₀ = 0.07 mg/kg p.o.) and citric acid-induced cough in rats (62-82% reduction at 0.3-10 mg/kg p.o.). In a phase II study in asthmatic patients, a single oral dose of 100 mg significantly antagonized the bronchoconstrictor response to neurokinin A and was well tolerated. Potentially useful for the treatment of asthma and rhinitis.

SOURCE – Novartis.

REFERENCES

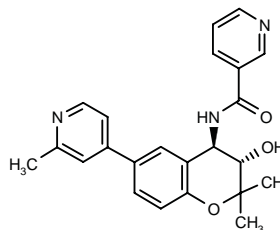
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- Joos, G. et al. *The effect of the dual NK1/NK2 tachykinin receptor antagonist DNK333A on neurokinin A-induced bronchoconstriction in patients with asthma*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A628.
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- Novartis Annual Report 2000.

*Identified compound **264027** (see **263290**) Drug Data Rep 1998, 020(06): 0492.

PKF-217-744***254531**

(+)-(3*S*,4*R*)-*N*-[3-Hydroxy-2,2-dimethyl-6-(2-methyl-4-pyridyl)-3,4-dihydro-2*H*-1-benzopyran-4-yl]pyridine-3-carboxamide

SDZ-217-744



C23 H23 N3 O3; Mol wt: 389.4580

ACTION – Potassium channel activator proven to open the recombinant vascular K_{ATP} channel Kir6.1/SUR2B and inhibit spontaneous activity of rat portal vein (ED₅₀ = 7.9 nM). Compound showed affinity for SUR2B channels (K_i = 26 nM) and was 6-fold more potent than levcromakalim. When administered intratracheally to guinea pigs or monkeys, it reversed airways hyperreactivity and protected against bronchoconstriction at doses not accompanied by cardiovascular effects. Potentially useful for the treatment of asthma.

SOURCE – Novartis.

REFERENCES

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- Manley, P.W. (Novartis Deutschland GmbH; Novartis AG) *2,2-Dialkyl- and 2,2-dialkyl-3, 4-dihydro-3-hydroxy-2*H*-1-benzopyrans, their use as pharmaceuticals*. EP 0623129, WO 9412493.
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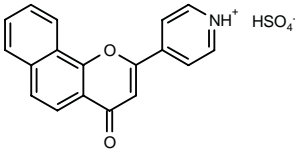
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TREATMENT OF CYSTIC FIBROSIS

UCCF-029

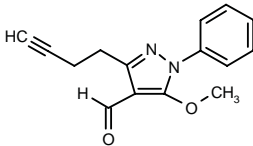
306063

4-(4-Oxo-4*H*-benzo[*h*]chromen-2-yl)pyridinium hydrogen sulfate



C18 H12 N O2 . H O4 S; Mol wt: 371.3677

ACTION – Potent activator of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel shown to be significantly more potent than genistein. Compound also induced strong Cl[–] currents in cell monolayers at concentrations below those required for genistein, was not cytotoxic and did not produce significant increases in intracellular cAMP concentrations or significant inhibition of phosphatase activity. Potentially useful for the treatment of cystic fibrosis. Another related compound is:



UCCF-180 [306064]: C15 H14 N2 O2

SOURCES – University of California, Davis, Davis, CA (US); University of California, San Francisco, San Francisco, CA (US).

REFERENCES

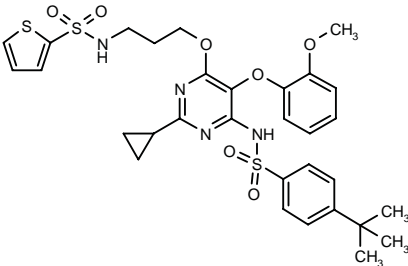
1. Galletta, L.J.V. et al. *Novel CFTR chloride channel activators identified by screening of combinatorial libraries based on flavone and benzoquinolinizinium lead compounds.* J Biol Chem 2001, 276(23): 19723.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

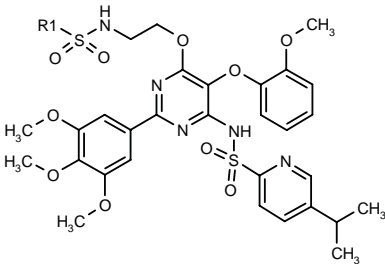
302488

N-[3-[6-(4-*tert*-Butylphenylsulfonamido)-2-cyclopropyl-5-(2-methoxyphenoxy)pyrimidin-4-yloxy]propyl]thiophene-2-sulfonamide



C31 H36 N4 O7 S3; Mol wt: 672.8444

ACTION– Endothelin receptor antagonist with preferential affinity for ET_B over ET_A receptors, as demonstrated in binding assays by respective IC₅₀ values of 14.8 and 1.86 nM against [¹²⁵I]-ET-1 binding to human ET_A and ET_B receptors cloned in CHO cells, as well as in functional assays by pA₂ values of 6.16 and 7.95, respectively, for inhibition of ET-1-induced contractions of isolated rat aortic rings (ET_A receptors) and rat tracheal rings (ET_B receptors). Potentially useful for the treatment of endothelin-mediated disorders, particularly circulatory disorders such as hypertension, ischemia, vasospasm and angina pectoris, proliferative disorders such as cancer, migraine and inflammatory disorders. Other exemplified compounds from this series of bis-sulfonamides include the following:



Compound	R1	Formula
302490	4-Me-Ph	C ₃₇ H ₄₁ N ₅ O ₁₀ S ₂
302492	2-thienyl	C ₃₄ H ₃₇ N ₅ O ₁₀ S ₃
302493	Pr	C ₃₃ H ₄₁ N ₅ O ₁₀ S ₂

SOURCE – Actelion.

REFERENCES

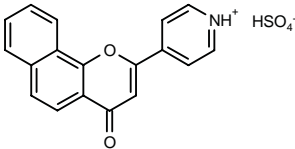
1. Bolli, M. et al. (Actelion Ltd.) *Bis-sulfonamides*. WO 0117976.

TREATMENT OF CYSTIC FIBROSIS

UCCF-029

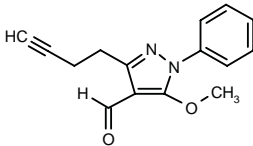
306063

4-(4-Oxo-4*H*-benzo[*h*]chromen-2-yl)pyridinium hydrogen sulfate



C18 H12 N O2 . H O4 S; Mol wt: 371.3677

ACTION – Potent activator of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel shown to be significantly more potent than genistein. Compound also induced strong Cl[–] currents in cell monolayers at concentrations below those required for genistein, was not cytotoxic and did not produce significant increases in intracellular cAMP concentrations or significant inhibition of phosphatase activity. Potentially useful for the treatment of cystic fibrosis. Another related compound is:



UCCF-180 [306064]: C15 H14 N2 O2

SOURCES – University of California, Davis, Davis, CA (US); University of California, San Francisco, San Francisco, CA (US).

REFERENCES

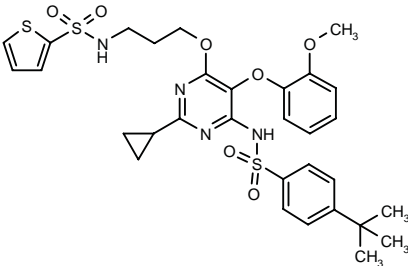
1. Galletta, L.J.V. et al. *Novel CFTR chloride channel activators identified by screening of combinatorial libraries based on flavone and benzoquinolinizinium lead compounds.* J Biol Chem 2001, 276(23): 19723.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

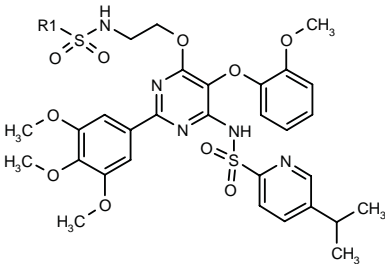
302488

N-[3-[6-(4-*tert*-Butylphenylsulfonamido)-2-cyclopropyl-5-(2-methoxyphenoxy)pyrimidin-4-yloxy]propyl]thiophene-2-sulfonamide



C31 H36 N4 O7 S3; Mol wt: 672.8444

ACTION– Endothelin receptor antagonist with preferential affinity for ET_B over ET_A receptors, as demonstrated in binding assays by respective IC₅₀ values of 14.8 and 1.86 nM against [¹²⁵I]-ET-1 binding to human ET_A and ET_B receptors cloned in CHO cells, as well as in functional assays by pA₂ values of 6.16 and 7.95, respectively, for inhibition of ET-1-induced contractions of isolated rat aortic rings (ET_A receptors) and rat tracheal rings (ET_B receptors). Potentially useful for the treatment of endothelin-mediated disorders, particularly circulatory disorders such as hypertension, ischemia, vasospasm and angina pectoris, proliferative disorders such as cancer, migraine and inflammatory disorders. Other exemplified compounds from this series of bis-sulfonamides include the following:



Compound	R1	Formula
302490	4-Me-Ph	C ₃₇ H ₄₁ N ₅ O ₁₀ S ₂
302492	2-thienyl	C ₃₄ H ₃₇ N ₅ O ₁₀ S ₃
302493	Pr	C ₃₃ H ₄₁ N ₅ O ₁₀ S ₂

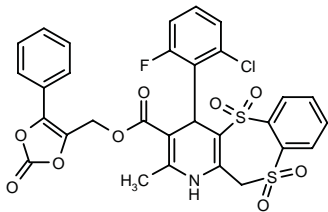
SOURCE – Actelion.

REFERENCES

1. Bolli, M. et al. (Actelion Ltd.) *Bis-sulfonamides*. WO 0117976.

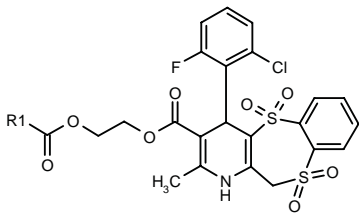
303146

4-(2-Chloro-6-fluorophenyl)-2-methyl-5,5,10,10-tetraoxo-4,11-dihydro-1*H*-[1,5]benzodithiepine[3,2-*b*]pyridine-3-carboxylic acid 2-oxo-5-phenyl-1,3-dioxol-4-ylmethyl ester



C30 H21 Cl F N O9 S2; Mol wt: 658.0769

ACTION – Calcium channel antagonist (IC₅₀ = 11 nM against [³H]-nitrendipine binding in rabbit heart preparations), potentially useful for the treatment or prevention of hypersensitivity, allergy, asthma, bronchospasm, dysmenorrhea, esophageal spasm, glaucoma, preterm labor, urinary tract disorders, gastrointestinal motility disorders and cardiovascular disorders. Other compounds from this series of benzo-fused dithiepine[6,5-*b*]pyridines include the following:



Compound	R1	Formula
303147	Ph	C ₂₉ H ₂₃ ClFNO ₈ S ₂
303148	cyclohexyl	C ₂₉ H ₂₉ ClFNO ₈ S ₂
303149	(CH ₂) ₆ Ph	C ₃₅ H ₃₅ ClFNO ₈ S ₂
303397	i-Pr	C ₂₆ H ₂₅ ClFNO ₈ S ₂

SOURCE – Ortho-McNeil.

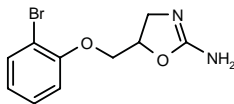
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1. Bullington, J.L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Benzo-fused dithiepine[6,5-*b*]pyridines, and related compsns. and methods.* WO 0121621.

S-23515³⁻⁷

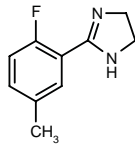
276475

5-(2-Bromophenoxymethyl)-4,5-dihydrooxazol-2-amine



C10 H11 Br N2 O2; Mol wt: 271.1129

ACTION – Imidazoline-like agent with high affinity for imidazoline I₁ versus imidazoline I₂ receptors (K_i = 6.40 and 403 nM, respectively) and > 4,000-fold selectivity over α₂-adrenoceptors. Compound exhibited central hypotensive activity in rabbits, inducing a dose-dependent decrease in blood pressure when administered intracisternally at doses of 10-30 μg/kg; this effect was antagonized by the imidazoline antagonist efaroxan but not by the α₂-adrenoceptor antagonist rauwolscine, and was potentiated by the selective α₂-adrenoceptor agonist α-methylnoradrenaline. Another imidazoline-like agent is:



S-23757 [304954]:^{1,2,4,6} C10 H11 F N2

SOURCE – Servier.

REFERENCES

1. Payard, M. et al. (ADIR et Cie.) *New imidazoline derivs. having activity for the imidazoline receptor.* EP 0846688, JP 1998168065, US 5925665.

2. Baurin, N. et al. *3D-QSAR CoMFA study on imidazolinergic I2 ligands: A significant model through a combined exploration of structural diversity and methodology.* J Med Chem 2000, 43(6): 1109.

3. Bousquet, P. et al. *A centrally acting hypotensive drug with a new pharmacological profile. Evidence for a synergistic interaction between imidazoline and α₂-adrenergic drugs.* FASEB J 2000, 14(8): Abst 30.

4. Bousquet, P. et al. *Imidazoline receptors: A challenge.* Pharm Acta Helv 2000, 74(2-3): 205.

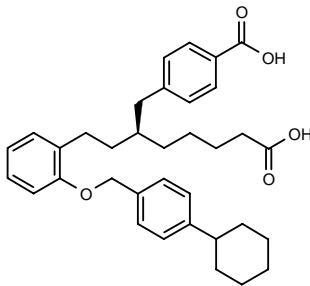
5. Bruban, V. et al. *Central blood pressure effects of S 23515, a ligand highly selective for imidazoline receptors over α₂-adrenoceptors.* Am J Hypertens 1999, 12(4, Part 2): 107A.

6. Bruban, V. et al. *Respective contributions of α-adrenergic and non-adrenergic mechanisms in the hypotensive effect of imidazoline-like drugs.* Br J Pharmacol 2001, 133(2): 261.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

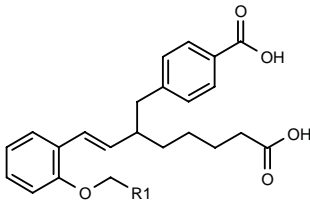
302849

4-[6-Carboxy-2(*S*)-[2-[2-(4-cyclohexylbenzyloxy)phenyl]ethyl]hexyl]benzoic acid



C35 H42 O5; Mol wt: 542.7118

ACTION – Agent for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and stroke, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis, fibrotic disorders, asthma and urogenital system disorders such as prostatic hypertrophy, erectile dysfunction and urinary incontinence that acts by directly stimulating soluble guanylate cyclase (sGC) and by increasing intracellular cGMP levels, as demonstrated *in vitro* using recombinant sGC at 0.1-10 µM. In addition, compound inhibited phenylephrine-induced contractions of rabbit saphenous vein strips (IC₅₀ = 0.2 nM). Other exemplified compounds from this series of dicarboxylic acid derivatives include the following:



Compound	R1	Formula
302855	4-Ph-Ph	C ₃₅ H ₃₄ O ₅
302858	C ₇ H ₁₅	C ₃₀ H ₄₀ O ₅
302859	4-cyclohexyl-Ph	C ₃₅ H ₄₀ O ₅
302860	1-[3,5-(Cl)2-Ph]-5-Me-3-pyrazolyl	C ₃₃ H ₃₂ Cl ₂ N ₂ O ₅
302861	2-benzothienyl	C ₃₁ H ₃₀ O ₅ S
302862	4-(2-CF3-4-thiazolyl)-Ph	C ₃₃ H ₃₀ F ₃ NO ₅ S

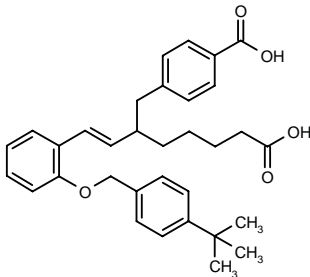
SOURCE – Bayer.

REFERENCES

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302863

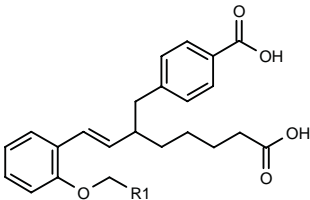
4-[4-[2-(4-*tert*-Butylbenzyloxy)phenyl]-2-(4-carboxybutyl)-3(*E*)-butenyl]benzoic acid



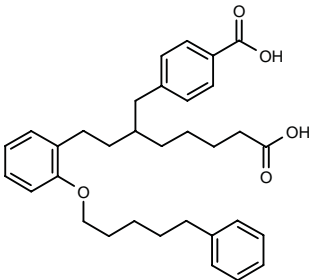
C33 H38 O5; Mol wt: 514.6582

ACTION – Agent for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and stroke, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis, fibrotic disorders, asthma and urogenital system disorders such as prostatic hypertrophy, erectile dysfunction and urinary incontinence that acts by directly stimulating soluble guanylate cyclase (sGC) and by increasing intracellular

cGMP levels, as demonstrated *in vitro* using recombinant sGC at 0.1-10 µM. In addition, compound inhibited phenylephrine-induced contractions of rabbit saphenous vein strips (IC₅₀ = 0.35 nM). Other exemplified compounds from this series of dicarboxylic acid derivatives include the following:



Compound	R1	Formula
302865	(CH ₂) ₄ Ph	C ₃₃ H ₃₈ O ₅
302867	2-Cl-Ph	C ₂₉ H ₂₉ ClO ₅
302869	4-Et-Ph	C ₃₁ H ₃₄ O ₅



302871: C33 H40 O5

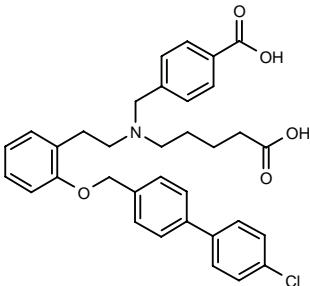
SOURCE – Bayer.

REFERENCES

1. Alonso-Alija, C. et al. (Bayer AG) *Novel derivs. of dicarboxylic acid having pharmaceutical properties.* WO 0119776.

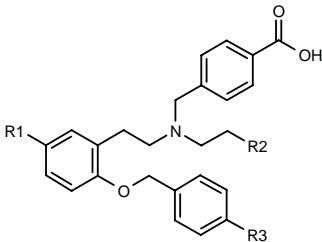
302875

4-[*N*-(4-Carboxybutyl)-*N*-[2-[2-(4'-chlorobiphenyl)-4-yl-methoxy]phenyl]ethyl]aminomethyl]benzoic acid



C34 H34 Cl N O5; Mol wt: 572.0976

ACTION – Agent for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and stroke, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis, fibrotic disorders, asthma and urogenital system disorders such as prostatic hypertrophy, erectile dysfunction and urinary incontinence that acts by directly stimulating soluble guanylate cyclase (sGC) and by increasing intracellular cGMP levels, as demonstrated *in vitro* using recombinant sGC at 0.1-10 µM. In addition, compound inhibited phenylephrine-induced contractions of rabbit saphenous vein strips (IC₅₀ = 0.5 nM). Other exemplified compounds from this series of dicarboxylic acid derivatives include the following:



Compound	R1	R2	R3	Formula
302877	H	CH2CH2CO2H	CH2CH2Ph	C ₃₆ H ₄₀ ClNO ₅
302880	H	CH2CH2CO2H	CH=CHPh	C ₃₆ H ₃₇ NO ₅
302882	H	CH2CH2CO2H	cyclohexyl	C ₃₄ H ₄₁ NO ₅
302885	H	CH2CH2CO2H	4-CF3-PhO	C ₃₆ H ₃₄ F ₃ NO ₆
302886	H	CH2CH2CO2H	4-MeO-Ph	C ₃₆ H ₃₇ NO ₆
302887	H	4-CO2H-PhO	cyclohexyl	C ₃₈ H ₄₁ NO ₆
302888	F	CH2CH2CO2H	4-CF3-Ph	C ₃₆ H ₃₃ F ₄ NO ₅

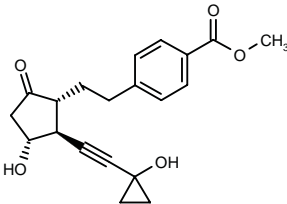
SOURCE – Bayer.

REFERENCES

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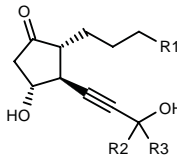
302988

4-[2-[(1*R*,2*S*,3*R*)-3-Hydroxy-2-[2-(1-hydroxycyclopropyl)-ethynyl]-5-oxocyclopentyl]ethyl]benzoic acid methyl ester



C20 H22 O5; Mol wt: 342.3888

ACTION – Prostaglandin E derivative that inhibits vascular smooth muscle cell proliferation and is therefore potentially useful for the treatment or prevention of vascular hypertrophy and obstruction and post-PTCA restenosis. Other exemplified compounds include the following:



Compound	R1	R2,R3	Formula
302989	4-(CO2Me)-PhCH2	-CH2CH2-	C ₂₂ H ₂₆ O ₅
302990	4-CO2H-Ph	-(CH2)3-	C ₂₁ H ₂₄ O ₅
302991	2-(CO2Me)-Ph	-(CH2)4-	C ₂₃ H ₂₈ O ₅
302992	3-CO2H-Ph	-(CH2)4-	C ₂₂ H ₂₆ O ₅
302993	4-(CO2Me)-PhCH2CH2	-(CH2)4-	C ₂₆ H ₃₂ O ₅
302994	4-CO2H-Ph	-(CH2)5-	C ₂₃ H ₂₆ O ₅
302995	4-(CO2Me)-Ph	-(CH2)7-	C ₂₈ H ₃₄ O ₅

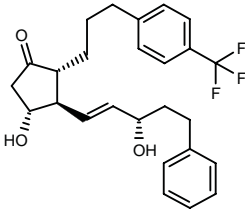
SOURCE – Taisho.

REFERENCES

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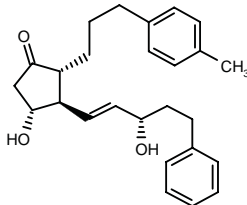
303050

4(*R*)-Hydroxy-3(*R*)-[3(*S*)-hydroxy-5-phenyl-1(*E*)-pentenyl]-2(*R*)-[3-[4-(trifluoromethyl)phenyl]propyl]-cyclopentanone



C26 H29 F3 O3; Mol wt: 446.5061

ACTION – Prostaglandin E₁ analogue that inhibits vascular smooth muscle cell proliferation, as demonstrated in human aorta-derived vascular cells (IC₅₀ = 0.66 µM). Potentially useful for the treatment or prevention of vascular hypertrophy and obstruction and post-PTCA restenosis. Another exemplified compound from this series of prostaglandin analogues is:



303051: C26 H32 O3

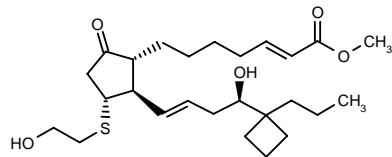
SOURCE – Taisho.

REFERENCES

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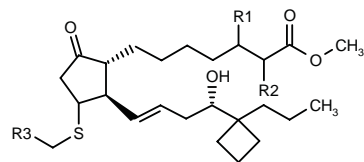
303052

7-[(1*R*,2*R*,3*R*)-3-(2-Hydroxyethylsulfanyl)-2-[4(*R*)-hydroxy-4-(1-propylcyclobutyl)-1(*E*)-butenyl]-5-oxocyclopentyl]-2(*E*)-heptenoic acid methyl ester



C26 H42 O5 S; Mol wt: 466.6788

ACTION – Prostaglandin E₁ derivative that inhibits vascular smooth muscle cell proliferation, as demonstrated in human aorta-derived vascular cells (100% inhibition at 10 μM). Potentially useful for the treatment or prevention of vascular hypertrophy and obstruction and post-PTCA restenosis. Other exemplified compounds include the following:



Compound	R1	R2	R3	Isomer	Formula
303053	H	H	CH2OH	3'S	C ₂₆ H ₄₄ O ₅ S
303054	bond		CH2OH	3'R	C ₂₆ H ₄₂ O ₅ S
303055	H	H	CH2CH2OH	3'R	C ₂₇ H ₄₆ O ₅ S
303057	H	H	(<i>R</i>)-CH(NH2)CO2Me	3'R	C ₂₈ H ₄₇ NO ₆ S
303058	H	H	(<i>R</i>)-CH(NH2)CO2Me	3'S	C ₂₈ H ₄₇ NO ₆ S

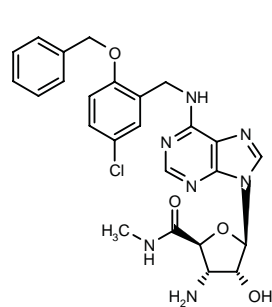
SOURCE – Taisho.

REFERENCES

1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin derivs.* WO 0119789.

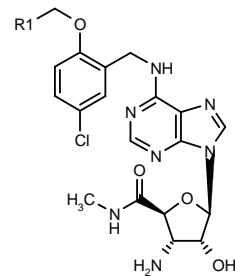
303348

3(*S*)-Amino-5(*R*)-[*N*⁶-[2-(benzyloxy)-5-chlorobenzyl]-adenin-9-yl]-4(*R*)-hydroxy-*N*-methyltetrahydrofuran-2(*S*)-carboxamide



C25 H26 Cl N7 O4; Mol wt: 523.9784

ACTION – Adenosine A₃ agonist, potentially useful for the treatment of ischemia, particularly perioperative myocardial ischemia. Other specifically claimed compounds are:



Compound	R1	Formula
303349	3-furyl	C ₂₃ H ₂₄ ClN ₇ O ₅
303350	2-furyl	C ₂₃ H ₂₄ ClN ₇ O ₅
303351	2-thiazolyl	C ₂₂ H ₂₃ ClN ₆ O ₄ S
303352	3-Me-5-isoxazolyl	C ₂₃ H ₂₅ ClN ₆ O ₅

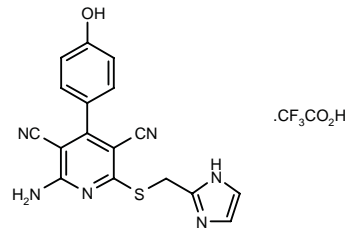
SOURCE – Pfizer.

REFERENCES

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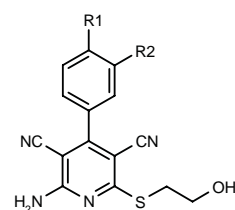
303438

2-Amino-4-(4-hydroxyphenyl)-6-(1*H*-imidazol-2-ylmethyl-sulfanyl)pyridine-3,5-dicarbonitrile trifluoroacetate



C17 H12 N6 O S . C2 H F3 O2; Mol wt: 462.4107

ACTION – Selective adenosine A_{2B} receptor agonist, as demonstrated *in vitro* in CHO cells stably transfected with the A₁, A_{2A} and A_{2B} receptors. In addition, compound exhibited coronary vasodilating effects in Langendorff perfused rat hearts (64% decrease in coronary perfusion pressure at 0.1 μg/ml). Potentially useful for the treatment of a broad range of conditions including cardiovascular diseases, urogenital tract diseases, respiratory tract diseases, inflammatory and neuroinflammatory diseases, diabetes, especially diabetes mellitus, neurodegenerative diseases, pain, cancer and liver fibrosis and cirrhosis. Other exemplified compounds from this series of substituted 2-thio-3,5-dicyano-4-aryl-6-aminopyridines include the following:



Compound	R1	R2	Formula
303440	H	OH	C ₁₅ H ₁₂ N ₄ O ₂ S
303441	OH	H	C ₁₅ H ₁₂ N ₄ O ₂ S

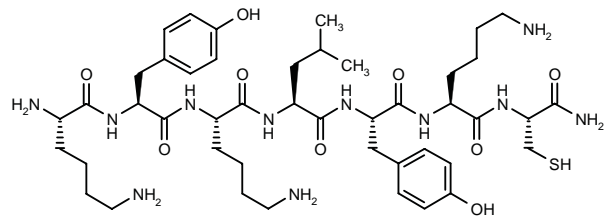
SOURCE – Bayer.

REFERENCES

1. Rosentreter, U. et al. (Bayer AG) *Substd. 2-thio-3,5-dicyano-4-aryl-6-aminopyridines and the use thereof.* WO 0125210.

303758

L-Lysyl-L-tyrosyl-L-lysyl-L-leucyl-L-tyrosyl-L-lysyl-L-cysteinamide



C45 H73 N11 O9 S; Mol wt: 944.2057

ACTION – Small peptide ligand that binds to the 5'-untranslated region of cholesterol ester transfer protein (CETP) mRNA ($K_d = 32 \mu\text{M}$). In transgenic mice expressing human-CETP, the peptide inhibited the translation of the CETP protein and at a dose of 100 mg/kg i.v. it produced a strong reduction in CETP activity. Potentially useful for the treatment of atherosclerosis.

SOURCE – Bayer.

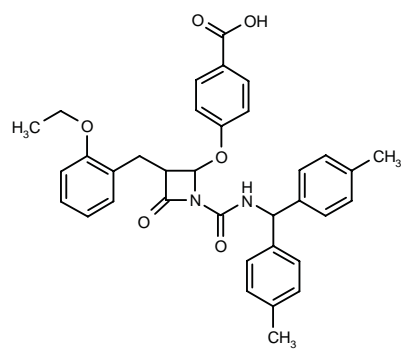
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1. Baumann, M. et al. *Combinatorial synthesis of cholesterol ester transfer protein-mRNA ligands and screening by nondenaturing gel-electrophoresis.* J Med Chem 2001, 44(13): 2172.

BCEAB

304946

4-[1-[N-[Bis(4-methylphenyl)methyl]carbamoyl]-3-(2-ethoxybenzyl)-4-oxoazetidin-2-yloxy]benzoic acid



C35 H34 N2 O6; Mol wt: 578.6616

ACTION – Potent and selective, orally active chymase inhibitor ($\text{IC}_{50} = 5.4 \text{ nM}$) with no activity against angiotensin-converting enzyme (ACE), elastase and trypsin. In isolated dog arteries, compound inhibited angiotensin I-induced vasoconstriction with an IC_{50} value of $2.8 \mu\text{M}$, and in hamsters it significantly suppressed heart chymase activity to 42% and 26.9% after oral doses of 100 and 300 mg/kg, respectively. Potentially useful for preventing tissue remodeling.

SOURCE – Shionogi.

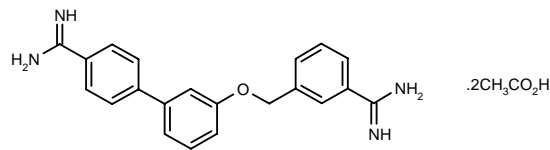
REFERENCES

1. Uenaka, M. et al. (Shionogi & Co. Ltd.) *Monocyclic β -lactam cpds. and chymase inhibitors containing the same.* EP 1099690, WO 0005204.
2. Takai, S. et al. *An orally active chymase inhibitor, BCEAB, suppresses heart chymase activity in the hamster.* Jpn J Pharmacol 2001, 86(1): 124.

EMD-221963

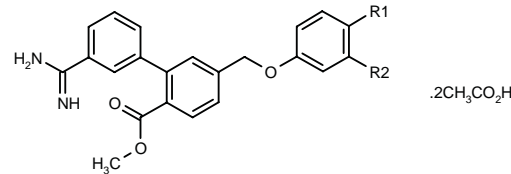
303097

3'-(3-Amidinobenzoyloxy)biphenyl-4-carboxamidinium diacetate



C21 H20 N4 O . 2 C2 H4 O2; Mol wt: 464.5192

ACTION – An inhibitor of the Na^+/H^+ exchanger subtype 3 (NHE-3), as demonstrated in LAP1 cells expressing human NHE-3 ($\text{IC}_{50} = 1 \mu\text{M}$), with potential for the treatment of thrombosis, ischemic disorders, stroke, shock states, proliferative disorders and renal disorders. Other compounds from this series of biphenyl derivatives include the following:



Compound	R1	R2	Formula
EMD-246326[303099]	C(=NH)NH2	H	C ₂₃ H ₂₂ N ₄ O ₃ .2C ₂ H ₄ O ₂
EMD-246327[303102]	H	C(=NH)NH2	C ₂₃ H ₂₂ N ₄ O ₃ .2C ₂ H ₄ O ₂

SOURCE – Merck KGaA.

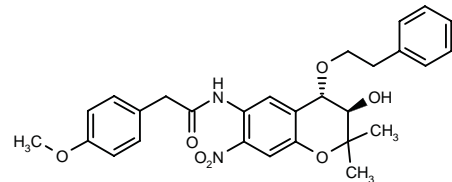
REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *Biphenyl derivs. used as NHE-3 inhibitors.* DE 19945302, WO 0121582.

ANTIARRHYTHMIC DRUGS

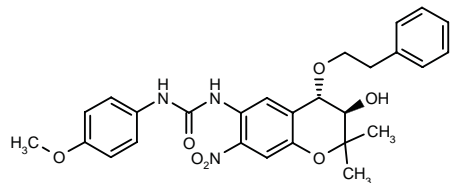
303209

trans-N-[3-Hydroxy-2,2-dimethyl-7-nitro-4-(2-phenylethoxy)-3,4-dihydro-2H-1-benzopyran-6-yl]-2-(4-methoxyphenyl)acetamide



C28 H30 N2 O7; Mol wt: 506.5520

ACTION – Antiarrhythmic agent that acts by prolonging the functional refractory period of atrial muscle ($EC_{20} = 2.4 \mu\text{M}$ in guinea pig left atrial muscle), without influencing the refractory period of ventricular muscle and action potential parameters, and which is thus expected to cause fewer side effects than conventional antiarrhythmic agents. Another compound from this series of 4-oxy-benzopyran derivatives is:



303210: C27 H29 N3 O7

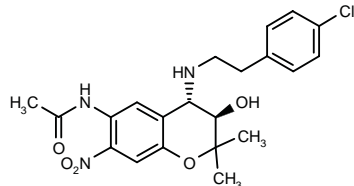
SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *4-Oxybenzopyran deriv.* JP 2001158780, WO 0121609.

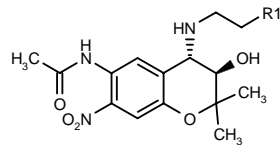
303211

trans-N-[4-[2-(4-Chlorophenyl)ethylamino]-3-hydroxy-2,2-dimethyl-7-nitro-3,4-dihydro-2*H*-1-benzopyran-6-yl]acetamide



C21 H24 Cl N3 O5; Mol wt: 433.8896

ACTION – Antiarrhythmic agent that acts by prolonging the functional refractory period of atrial muscle ($EC_{20} = 1.4 \mu\text{M}$ in guinea pig left atrial muscle), without influencing the refractory period of ventricular muscle and action potential parameters, and which is thus expected to cause fewer side effects than conventional antiarrhythmic agents. Other exemplified compounds from this series of 4-aminobenzopyran derivatives include the following:



Compound	R1	Formula
303212	Ph	C ₂₁ H ₂₅ N ₃ O ₅
303213	CH ₂ CH ₂ Ph	C ₂₃ H ₂₉ N ₃ O ₅
303214	4-OH-Ph	C ₂₁ H ₂₅ N ₃ O ₆
303215	4-MeO-Ph	C ₂₂ H ₂₇ N ₃ O ₆
303216	4-NO ₂ -Ph	C ₂₁ H ₂₄ N ₄ O ₇

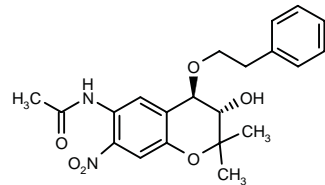
SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Benzopyran deriv.* JP 2001151767, WO 0121610.

303424

trans-N-[3-Hydroxy-2,2-dimethyl-7-nitro-4-(2-phenylethoxy)-3,4-dihydro-2*H*-1-benzopyran-6-yl]acetamide



C21 H24 N2 O6; Mol wt: 400.4286

ACTION – Antiarrhythmic agent that acts by prolonging the functional refractory period of atrial muscle ($EC_{20} = 2.1 \mu\text{M}$ in guinea pig left atrial muscle), without influencing the refractory period of ventricular muscle and action potential parameters, and which is thus expected to cause fewer side effects than conventional antiarrhythmic agents. A representative compound from a series of 4-oxybenzopyran derivatives.

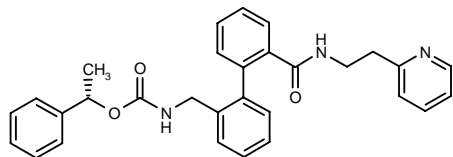
SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *4-Oxybenzopyran deriv.* JP 2001172275, WO 0125224.

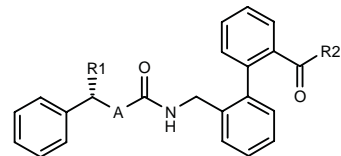
303428

N-[2'-[*N*-[2-(2-Pyridyl)ethyl]carbamoyl]biphenyl-2-yl-methyl]carbamic acid 1(*S*)-phenylethyl ester



C30 H29 N3 O3; Mol wt: 479.5771

ACTION – Antiarrhythmic agent, particularly useful for the treatment and prophylaxis of atrial arrhythmias such as atrial fibrillation or atrial flutter, that acts by blocking potassium Kv1.5 channels ($IC_{50} = 0.2 \mu\text{M}$ in *Xenopus* oocytes expressing the human Kv1.5 channel). Other exemplified compounds from this series of 2'-substituted 1,1'-biphenyl-2-carbonamides include the following:



Compound	R1	R2	A	Formula
303431	H	-L-Leu-NH ₂	O	C ₂₈ H ₃₁ N ₃ O ₄
303432	Me	2-Pyr-CH ₂ CH ₂ NH	CH ₂	C ₃₁ H ₃₁ N ₃ O ₂
303433	Me	(<i>S</i>)-NHCH ₂ CH(OH)Me	O	C ₂₆ H ₂₈ N ₂ O ₄

SOURCE – Aventis Pharma.

REFERENCES

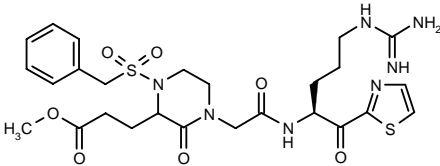
1. Brendel, J. et al. (Aventis Pharma Deutschland GmbH) *2'-Substd. 1,1'-biphenyl-2-carbonamides, method for the production thereof, use thereof as a medicament and pharmaceutical preparations containing said cpds..* DE 19947457, WO 0125189.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

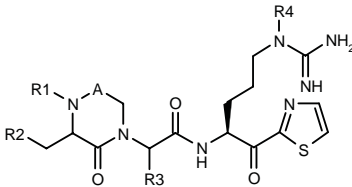
302169

3-[1-(Benzylsulfonyl)-4-[N-[4-guanidino-1(S)-(thiazol-2-ylcarbonyl)butyl]carbamoylmethyl]-3-oxopiperazin-2-yl]-propionic acid methyl ester

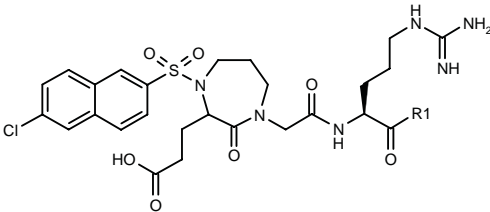


C26 H35 N7 O7 S2; Mol wt: 621.7365

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of factor Xa. Other exemplified compounds from this series of cyclic diaza compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
302172	4-Ph-PhSO2	CH2CO2Me	H	H	CH2	C ₃₁ H ₃₇ N ₇ O ₇ S ₂
302173	4-[NH2C(=NH)-NHCH2]-PhCH2CO	CO2Et	H	H	CH2	C ₂₉ H ₄₀ N ₁₀ O ₆ S
302174	4-Pip-CH2CH2	4-Pyr-CH2-NHCOCH2	H	H	CO	C ₃₁ H ₄₄ N ₁₀ O ₅ S
302175	SO2CH2Ph	CH2CO2H	H	H	CO	C ₂₅ H ₃₁ N ₇ O ₆ S ₂
302179	3-Ph-PhSO2	t-BuNH-COCH2	i-Pr	Me	CH2	C ₃₈ H ₅₂ N ₈ O ₆ S ₂



Compound	R1	Formula
302176	B(OH)2	C ₂₅ H ₃₄ BClN ₆ O ₆ S
302178	5-CF3-1,2,4-oxadiazol-3-yl	C ₂₉ H ₃₂ ClF ₃ N ₈ O ₆ S

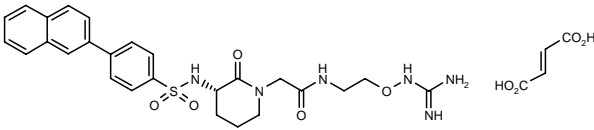
SOURCE – COR Therapeutics.

REFERENCES

1. Scarborough, R.M. et al. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors.* US 6204268.

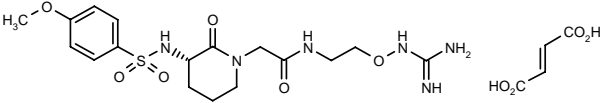
302627

N-[2-(Guanidinooxy)ethyl]-2-[3(S)-[4-(2-naphthyl)phenyl-sulfonamido]-2-oxopiperidin-1-yl]acetamide fumarate



C26 H30 N6 O5 S . C4 H4 O4; Mol wt: 654.6976

ACTION – Serine protease inhibitor, particularly active against factor Xa, that gave K_i values of 6.4 and 0.36 μM against thrombin and factor Xa, respectively. Potentially useful for the treatment of thrombosis, ischemia, stroke, restenosis or inflammation. Another exemplified azacycloalkanone derivative is:



302626: C17 H26 N6 O6 S . C4 H4 O4

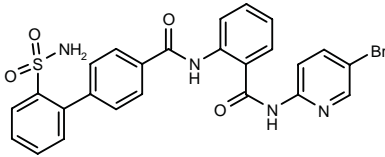
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Miller, S.C. et al. (3-Dimensional Pharmaceuticals, Inc.) *Azacycloalkanone serine protease inhibitors.* WO 0119795.

302804

N-[2-[N-(5-Bromopyridin-2-yl)carbamoyl]phenyl]-2'-sulfamoylbiphenyl-4-carboxamide



C25 H19 Br N4 O4 S; Mol wt: 551.4191

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of factor Xa either isolated or when assembled in the prothrombinase complex. Other specifically claimed compounds from this series of benzamide derivatives include the following:

SOURCE – Aventis Pharma.

REFERENCES

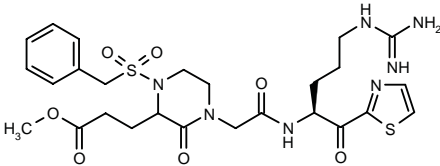
1. Brendel, J. et al. (Aventis Pharma Deutschland GmbH) *2'-Substd. 1,1'-biphenyl-2-carbonamides, method for the production thereof, use thereof as a medicament and pharmaceutical preparations containing said cpds..* DE 19947457, WO 0125189.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

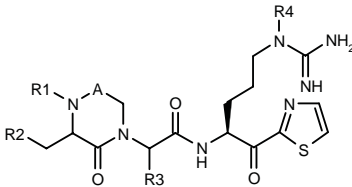
302169

3-[1-(Benzylsulfonyl)-4-[N-[4-guanidino-1(S)-(thiazol-2-ylcarbonyl)butyl]carbamoylmethyl]-3-oxopiperazin-2-yl]-propionic acid methyl ester

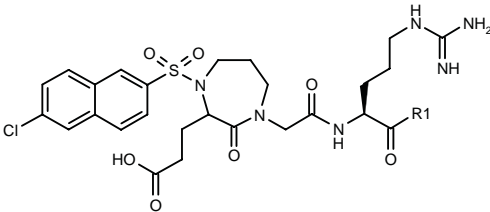


C26 H35 N7 O7 S2; Mol wt: 621.7365

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of factor Xa. Other exemplified compounds from this series of cyclic diaza compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
302172	4-Ph-PhSO2	CH2CO2Me	H	H	CH2	C ₃₁ H ₃₇ N ₇ O ₇ S ₂
302173	4-[NH2C(=NH)-NHCH2]-PhCH2CO	CO2Et	H	H	CH2	C ₂₉ H ₄₀ N ₁₀ O ₆ S
302174	4-Pip-CH2CH2	4-Pyr-CH2-NHCOCH2	H	H	CO	C ₃₁ H ₄₄ N ₁₀ O ₅ S
302175	SO2CH2Ph	CH2CO2H	H	H	CO	C ₂₅ H ₃₁ N ₇ O ₆ S ₂
302179	3-Ph-PhSO2	t-BuNH-COCH2	i-Pr	Me	CH2	C ₃₈ H ₅₂ N ₈ O ₆ S ₂



Compound	R1	Formula
302176	B(OH)2	C ₂₅ H ₃₄ BClN ₆ O ₆ S
302178	5-CF3-1,2,4-oxadiazol-3-yl	C ₂₉ H ₃₂ ClF ₃ N ₈ O ₆ S

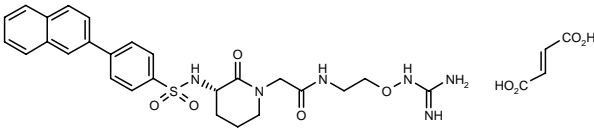
SOURCE – COR Therapeutics.

REFERENCES

1. Scarborough, R.M. et al. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors.* US 6204268.

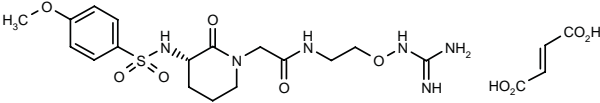
302627

N-[2-(Guanidinooxy)ethyl]-2-[3(S)-[4-(2-naphthyl)phenyl-sulfonamido]-2-oxopiperidin-1-yl]acetamide fumarate



C26 H30 N6 O5 S . C4 H4 O4; Mol wt: 654.6976

ACTION – Serine protease inhibitor, particularly active against factor Xa, that gave K_i values of 6.4 and 0.36 μM against thrombin and factor Xa, respectively. Potentially useful for the treatment of thrombosis, ischemia, stroke, restenosis or inflammation. Another exemplified azacycloalkanone derivative is:



302626: C17 H26 N6 O6 S . C4 H4 O4

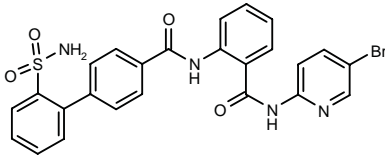
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Miller, S.C. et al. (3-Dimensional Pharmaceuticals, Inc.) *Azacycloalkanone serine protease inhibitors.* WO 0119795.

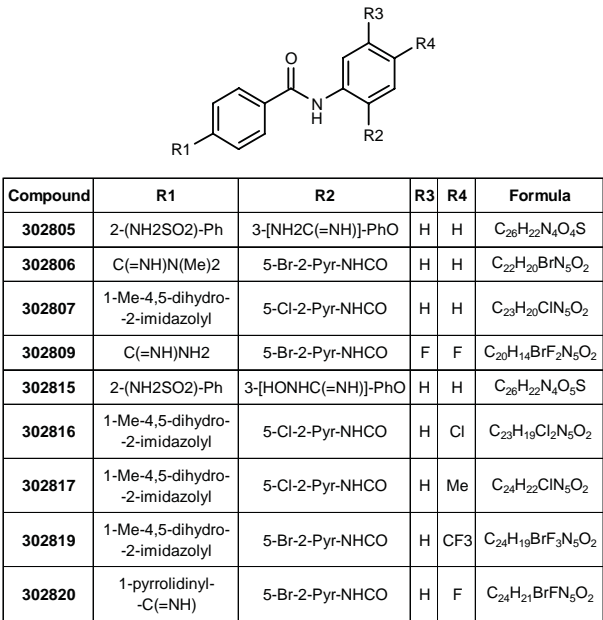
302804

N-[2-[N-(5-Bromopyridin-2-yl)carbamoyl]phenyl]-2'-sulfamoylbiphenyl-4-carboxamide



C25 H19 Br N4 O4 S; Mol wt: 551.4191

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of factor Xa either isolated or when assembled in the prothrombinase complex. Other specifically claimed compounds from this series of benzamide derivatives include the following:



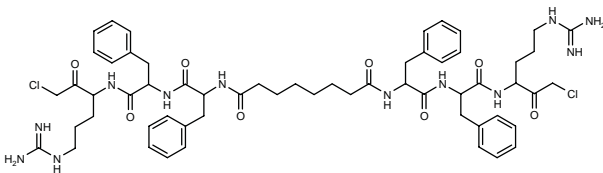
SOURCE – COR Therapeutics.

REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Benzamides and related inhibitors of factor Xa*. WO 0119788, WO 0119798.

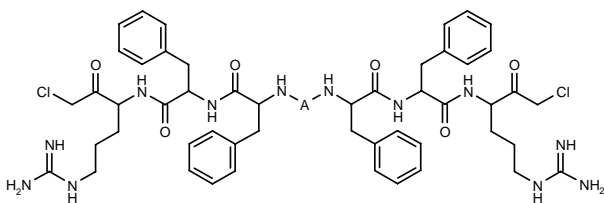
303041

N,N'-Bis[1-benzyl-2-[1-benzyl-2-[1-(2-chloroacetyl)-4-guanidinobutylamino]-2-oxoethylamino]-2-oxoethyl]-octanediamide



C58 H76 Cl2 N12 O8; Mol wt: 1140.2200

ACTION – A representative compound from a series of bivalent inhibitors of factor VIIa (FVIIa) and factor Xa (FXa), shown to selectively inhibit the protease activity of FVIIa and FXa when associated with tissue factor (TF) in the FVIIa/TF/FXa complex and reported to provide higher potency, enhanced specificity and reduced toxic effects when compared to inhibitors targeting the free form of each of these serine proteases. Potentially useful for the treatment or prevention of FVIIa/TF-related diseases such as deep vein thrombosis, arterial thrombosis, postsurgical thrombosis, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), stroke, tumor metastasis, inflammation, septic shock, hypotension, adult respiratory distress syndrome (ARDS), pulmonary embolism, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition, myocardial infarction and angiogenesis, as well as for the prophylaxis of individuals with atherosclerotic vessels at risk for thrombosis. Other exemplified compounds are:



Compound	A	Formula
303042	-COCO-	C ₅₂ H ₆₄ Cl ₂ N ₁₂ O ₈
303043	-COCH(OH)CH(OH)CO-	C ₅₄ H ₆₈ Cl ₂ N ₁₂ O ₁₀
303044	-CO(CH2)3CO-	C ₅₅ H ₇₀ Cl ₂ N ₁₂ O ₈

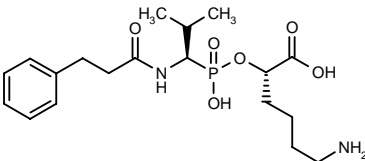
SOURCE – Novo Nordisk.

REFERENCES

1. Freskgaard, P.-O. and Jakobsen, P. (Novo Nordisk A/S) *Bivalent inhibitor of FVIIa/TF/FXa complex*. WO 0121661.

303140

6-Amino-2-(*S*)-[(hydroxy)[1-(*R*)-(3-phenylpropionamido)-2-methylpropyl]phosphoryloxy]hexanoic acid



C19 H31 N2 O6 P; Mol wt: 414.4359

ACTION – A representative compound from a series of phosphonic acid derivatives having carboxypeptidase B-inhibitory activity (> 90% inhibition at 500 nM in human plasma). No toxicity was observed in mice following administration of 1 g/kg i.v. Potentially useful for the treatment of thrombotic disorders, as well as diabetes, hyperlipidemia and inflammation.

SOURCE – Meiji Seika.

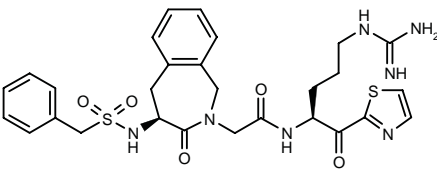
REFERENCES

1. Fushihara, K. et al. (Meiji Seika Kaisha, Ltd.) *Phosphonic acid derivs. having carboxypeptidase B inhibitory activity*. WO 0119836.

303164

2-[*N*^α-[2-[4(*S*)-(Benzylsulfonamido)-3-oxo-2,3,4,5-tetrahydro-1*H*-2-benzazepin-2-yl]acetyl]-L-arginyl]thiazole

2-[4(*S*)-(Benzylsulfonamido)-3-oxo-2,3,4,5-tetrahydro-1*H*-2-benzazepin-2-yl]-*N*-[4-guanidino-1(*S*)-(thiazol-2-ylcarbonyl)butyl]acetamide



C28 H33 N7 O5 S2; Mol wt: 611.7447

ACTION – A selective inhibitor of factor Xa, potentially useful as an antithrombotic agent and as a diagnostic reagent for coagulation disorders.

SOURCE – COR Therapeutics.

REFERENCES

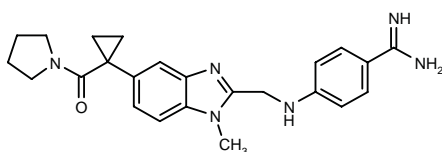
1. Zhu, B.-Y. and Scarborough, R. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors*. US 6218382.

BIBM-1015*,1-3

285207

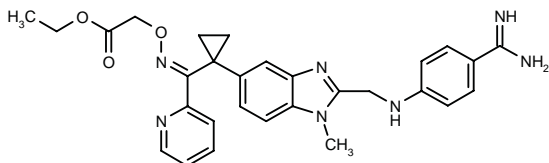
4-[1-Methyl-5-[1-(pyrrolidin-1-ylcarbonyl)cyclopropyl]-1*H*-benzimidazol-2-ylmethylamino]benzamidide

BIBM-1015CL

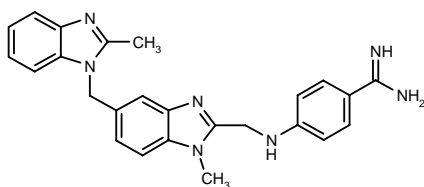


C24 H28 N6 O; Mol wt: 416.5262

ACTION – Anticoagulant, a dual inhibitor of thrombin and factor Xa ($K_i = 20$ and 15 nM, respectively) with high selectivity over other proteases including trypsin, plasmin, factor Xa and two-chain urokinase ($K_i = 102$, $13,000$, $8,200$ and $6,500$ nM, respectively). Potentially useful for the treatment of venous and arterial thrombosis. Other related compounds are:



BIBR-1109 [305849]:^{1,2} C29 H31 N7 O3



BIBT-0871 [305850]:^{1,2} C25 H25 N7

SOURCE – Boehringer Ingelheim.

REFERENCES

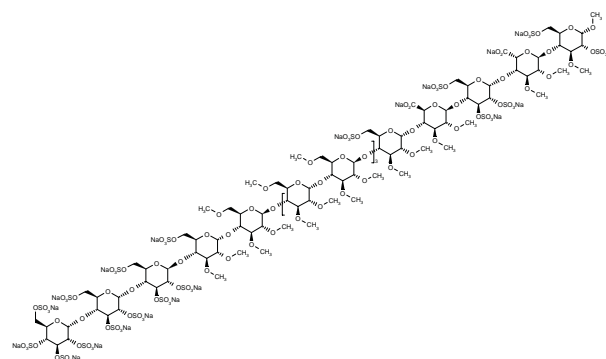
1. Ries, U. et al. (Boehringer Ingelheim Pharma KG) *Benzimidazoles, production thereof and use thereof as medicaments*. DE 19829964, EP 1095025, WO 0001704.
2. Nar, H. et al. *Structural basis for inhibition promiscuity of dual specific thrombin and factor Xa blood coagulation inhibitors*. *Structure* 2001, 9(1): 29.
3. Stassen, J.M. et al. *Design, synthesis and comparative biological properties of heterocyclic dual direct thrombin and factor Xa inhibitors*. *Thromb Haemost* 2001, (Suppl.): Abst P758.

*Identified compound **285207** Drug Data Rep 2000, 022(04): 0334.

SR-123781A

279698

Methyl *O*-2,3,4,6-tetra-*O*-sulfo- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3,6-tri-*O*-sulfo- β -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3-di-*O*-methyl-6-*O*-sulfo- α -D-glucopyranosyl-(1 \rightarrow 4)-[*O*-2,3,6-tri-*O*-methyl- β -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3,6-tri-*O*-methyl- α -D-glucopyranosyl-(1 \rightarrow 4)]₃-*O*-2,3,6-tri-*O*-methyl- β -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3-di-*O*-methyl-6-*O*-sulfo- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3-di-*O*-methyl- β -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-2,3-di-*O*-methyl- α -L-idopyranosyl-(1 \rightarrow 4)-3-*O*-methyl- α -D-glucopyranoside bis(hydrogen sulfate) nonadecasodium salt



C127 H201 Na19 O134 S17; Mol wt: 4853.7830

ACTION – Synthetic heparin mimetic, a hexadecasaccharide comprising an antithrombin (AT)-binding domain, a thrombin-binding domain and a neutral methylated heptasaccharide sequence. It showed high affinity for human AT ($K_d = 58$ nM) and potent inhibitory activity against factor Xa and thrombin ($IC_{50} = 77$ and 4.0 ng/ml, respectively). Compound also inhibited thrombin generation in human plasma ($IC_{50} = 0.09$ - 0.15 ng/ml) and did not compete for [3 H]-heparin binding to platelet factor 4 (PF4). Intravenous administration of compound in rats, rabbits or baboons produced prolonged anti-factor Xa and anti-factor IIa activity *ex vivo*. Compound strongly inhibited thrombus formation in experimental rat models of thrombosis such as thromboplastin-induced venous thrombosis ($ED_{50} = 18$ μ g/kg i.v.) and the arteriovenous shunt model ($ED_{50} = 225$ μ g/kg i.v.). In a model of arterial thrombosis in pigs where thrombus formation was induced by exposing human type III collagen to native blood *ex vivo*, compound (1-30 nmol/kg i.v.) induced significant inhibition of thrombus size and platelet adhesion and was more effective than heparin. Compound also had a more favorable pharmacokinetic profile compared to heparin. Potentially useful for the treatment or prevention of thrombotic diseases.

SOURCE – Sanofi-Synthelabo.

REFERENCES

1. Dreef-Tromp, C. et al. (Akzo Nobel N.V.; Sanofi-Synthelabo) *Synthetic polysaccharides, their method of production and pharmaceutical compositions containing same*. FR 2773804, WO 9936443.
2. Bal dit Sollier, C. et al. *A new synthetic heparin mimetic, SR123781A, exerts an antithrombotic activity in a pig model at picomolar concentrations*. *Thromb Haemost* 2001, (Suppl.): Abst OC1765.
3. Hérault, J.P. et al. *Effect of SR123781A, a synthetic heparin mimetic, on clot-bound thrombin and factor Xa in vitro and in vivo*. *Thromb Haemost* 2001, (Suppl.): Abst OC1702.

4. Herbert, J.M. et al. *SR123781A, a synthetic heparin mimetic*. Thromb Haemost 1999, (Suppl.): Abst 1312.

5. Herbert, J.M. et al. *SR123781A, a synthetic heparin mimetic*. Thromb Haemost 2001, 85(5): 852.

hATR-5

305819

Humanized anti-human tissue factor (TF) monoclonal antibody

ACTION – Humanized anti-human tissue factor (TF) antibody proven to inhibit TF-initiated coagulation *in vivo* in a model of TF- or lipopolysaccharide (LPS)-induced hypercoagulability in rats or cynomolgus monkeys. This antibody improved plasma levels of fibrinogen by inhibiting fibrin generation and consumption of several coagulation factors. Potentially useful for the treatment of hypercoagulability states such as disseminated intravascular coagulation.

SOURCE – Chugai.

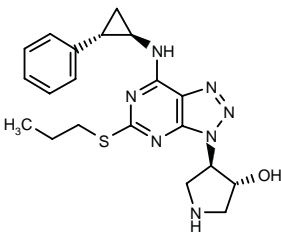
REFERENCES

1. Kitazawa, T. et al. *Humanized anti-human tissue factor antibody; Effects on hypercoagulable states in a human tissue factor-induced rat model and in a LPS-induced primate model*. Thromb Haemost 2001, (Suppl.): Abst OC162.

ANTIPLATELET THERAPY

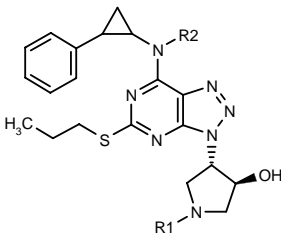
302746

4(R)-[7-[(1R,2S)-2-Phenylcyclopropylamino]-5-(propylsulfanyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-pyrrolidin-3(R)-ol



C20 H25 N7 O S; Mol wt: 411.5315

ACTION – Antithrombotic agent, a P_{2T} (also known as P2Y₁₂, P2Y_{ADP} or P_{2TAC}) receptor antagonist, claimed for the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischemic attacks, peripheral vascular disease and stable and unstable angina. Other specifically claimed compounds from this series of hydroxypyrrolidine derivatives are:



Compound	R1	R2	Isomer	Formula
302748	t-BuOCO	H	1R,2S	C ₂₈ H ₃₃ N ₇ O ₃ S
302751	t-BuOCO	H	1S,2R	C ₂₈ H ₃₃ N ₇ O ₃ S
302752	H	H	1R,2S	C ₂₀ H ₂₅ N ₇ OS
302754	H	Me	1R,2S	C ₂₁ H ₂₇ N ₇ OS
302756	CH ₂ CH ₂ OH	H	1R,2S	C ₂₂ H ₂₉ N ₇ O ₂ S
302758	CH ₂ Ph	H	1R,2S	C ₂₇ H ₃₁ N ₇ OS
302759	Ac	H	1R,2S	C ₂₂ H ₂₇ N ₇ O ₂ S

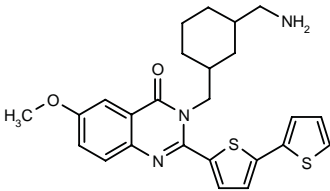
SOURCE – AstraZeneca.

REFERENCES

1. Teobald, B.J. (AstraZeneca plc) *Novel cpds*. WO 0119826.

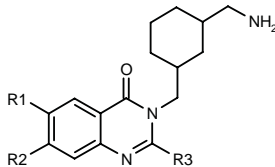
303336

3-[3-(Aminomethyl)cyclohexylmethyl]-2-(2,2'-bithien-5-yl)-6-methoxyquinazolin-4(3H)-one



C25 H27 N3 O2 S2; Mol wt: 465.6393

ACTION – Adhesion receptor antagonist, particularly glycoprotein IbIX (gplbIX) antagonist, that is potentially useful for the treatment of thrombotic disorders and conditions derived therefrom such as myocardial infarction, arteriosclerosis, angina pectoris, acute coronary syndrome, peripheral circulatory disorders, stroke and restenosis following angioplasty. Other specifically claimed quinazolinones are:



Compound	R1	R2	R3	Formula
303337	OMe	H	1-Naph	C ₂₇ H ₂₉ N ₃ O ₂
303338	Me	H	1-Naph	C ₂₇ H ₂₉ N ₃ O
303339	H	H	1-Naph	C ₂₆ H ₂₇ N ₃ O
303340	OMe	H	2-Naph	C ₂₇ H ₂₉ N ₃ O ₂
303341	H	H	2-Naph	C ₂₆ H ₂₇ N ₃ O
303342	Me	H	2-Naph	C ₂₇ H ₂₉ N ₃ O
303343	Cl	H	2-Naph	C ₂₆ H ₂₆ ClN ₃ O
303344	H	Cl	2-Naph	C ₂₆ H ₂₆ ClN ₃ O

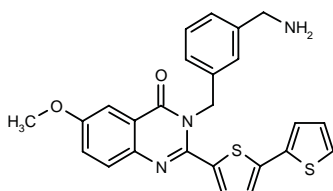
SOURCE – Merck KGaA.

REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) *Quinazolinones*. WO 0123364.

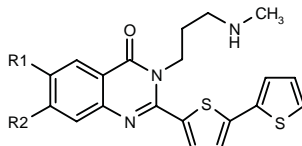
303345

3-[3-(Aminomethyl)benzyl]-2-(2,2'-bithien-5-yl)-6-methoxyquinazolin-4(3*H*)-one



C25 H21 N3 O2 S2; Mol wt: 459.5919

ACTION – Adhesion receptor antagonist, particularly glycoprotein IbIX (gplbIX) antagonist, that is potentially useful for the treatment of thrombotic disorders and conditions derived therefrom such as myocardial infarction, arteriosclerosis, angina pectoris, acute coronary syndrome, peripheral circulatory disorders, stroke and restenosis following angioplasty. Other specifically claimed quinazolinones are:



Compound	R1	R2	Formula
303346	Cl	H	C ₂₀ H ₁₈ ClN ₃ OS ₂
303347	H	Cl	C ₂₀ H ₁₈ ClN ₃ OS ₂

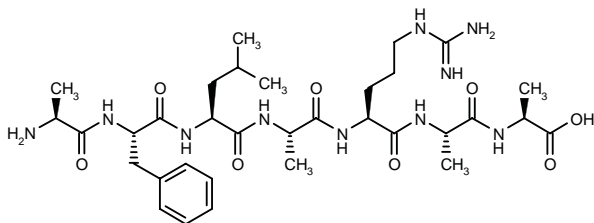
SOURCE – Merck KGaA.

REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) *Quinazolinones*. WO 0123365.

303425

L-Alanyl-L-phenylalanyl-L-leucyl-L-alanyl-L-arginyl-L-alanyl-L-alanine



C33 H54 N10 O8; Mol wt: 718.8516

ACTION – Peptide analogue of thrombin receptor-activating peptide (TRAP) with weak inhibitory activity against TRAP-induced platelet aggregation (IC₅₀ = 16-33 μM). Compound also antagonized platelet aggregation induced by α-thrombin, but not by ADP or collagen. Moreover, this peptide inhibited both thrombin- and TRAP-induced smooth muscle cell proliferation, probably by desensitizing the thrombin receptor. In a model of arterial thrombosis in rabbits induced by application of electrical current to the carotid artery, compound given as a bolus dose of 100 μmol/kg i.v. followed by 900 μmol/kg for 180 min significantly inhibited thrombus formation without altering hemostatic parameters. Potentially useful for the prevention of thrombosis and atherosclerosis.

SOURCE – University of Texas System, Austin, TX (US).

REFERENCES

1. Pakala, R. et al. *A peptide analogue of thrombin receptor-activating peptide inhibits thrombin-receptor-activating peptide-induced vascular smooth muscle cell proliferation*. J Cardiovasc Pharmacol 2001, 37(5): 619.

2. Pakala, R. et al. *A peptide ligand of the human thrombin receptor antagonizes thrombin receptor activating peptide and α-thrombin-induced platelet aggregation*. Fibrinolysis Proteolysis 2000, 14(1): 15.

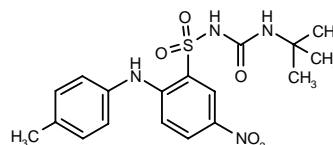
3. Pakala, R. et al. *Inhibition of arterial thrombosis by a peptide ligand of the thrombin receptor*. Thromb Res 2000, 100(1): 89.

BM-573

305698

N-(*tert*-Butylcarbamoyl)-2-(4-methylphenylamino)-5-nitrobenzenesulfonamide

N-*tert*-Butyl-*N*'-[2-(4-methylphenylamino)-5-nitrophenyl-sulfonyl]urea



C18 H24 N4 O5 S; Mol wt: 408.4766

ACTION – Antiplatelet agent, a torasemide derivative with thromboxane A₂ (TxA₂) TP receptor-antagonist activity superior to sulotroban and SQ-29548 (IC₅₀ = 0.3, 930 and 21 nM, respectively, for affinity to TxA₂ in human washed platelets), and thromboxane synthase-inhibitory activity. Compound prevented human platelet aggregation induced by arachidonic acid (ED₁₀₀ = 0.25 μM), U-46619 (ED₅₀ = 0.240 μM) and collagen (36.6% inhibition at 10 μM), and it completely prevented the production of TxA₂ by platelets activated by arachidonic acid, an effect independent of cyclooxygenase inhibition.

SOURCES – University of Liège, Liège (BE); University of Namur, Namur (BE).

REFERENCES

1. Dogné, J.-M.P.N. et al. *Design and pharmacological evaluation of an original non-carboxylic thromboxane A₂ receptor antagonist and thromboxane synthase inhibitor as promising antiplatelet agent*. Thromb Haemost 2001, (Suppl.): Abst P1630.

82D6A3**305822****Anti-human von Willebrand factor (vWF) monoclonal antibody**

ACTION – Antithrombotic agent, an anti-human vWF (von Willebrand factor) monoclonal antibody (MAb) that inhibits vWF binding to fibrillar collagen type I and III by binding to the vWF A3 domain. In a thrombosis model in baboons, doses of 300 and 600 µg/kg of the MAb abolished platelet thrombus formation but did not affect platelet count or coagulation parameters; bleeding time was only slightly prolonged.

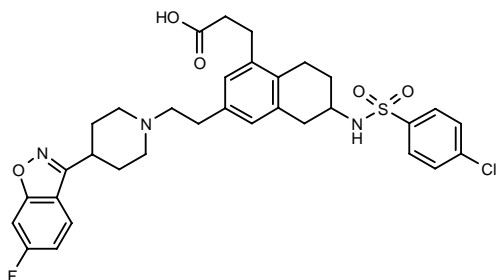
SOURCES – University of the Free State, Bloemfontein (ZA); Katholieke Universiteit Leuven, Leuven (BE).

REFERENCES

1. Hoylaerts, M.F. et al. *Von Willebrand factor binds to native collagen VI primarily via its A1 domain*. *Biochem J* 1997, 324(Part 1): 185.
2. Vanhoorelbeke, K. et al. *Inhibition of the VWF-collagen interaction by anti-human VWF antibody (82D6A3) results in abolition of in vivo arterial platelet thrombus formation in baboons*. *Thromb Haemost* 2001, (Suppl.): Abst OC158.

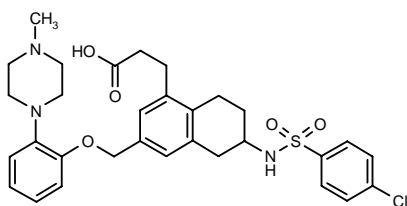
S-35120¹⁻³**305661**

3-[6-(4-Chlorophenylsulfonamido)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-5,6,7,8-tetrahydronaphthalen-1-yl]propionic acid



C33 H35 Cl F N3 O5 S; Mol wt: 640.1725

ACTION – Dual thromboxane A₂ (TxA₂) TP receptor and 5-HT_{2A} receptor antagonist, as demonstrated by inhibition of U-46619-induced contractions of rabbit saphenous vein (pA₂ = 8.6) and 5-HT-induced contractions of rabbit aorta (pA₂ = 7.5), as well as of U-46619- and 5-HT-induced human platelet aggregation (IC₅₀ = 0.26 and 1.2 µM, respectively). *In vivo*, compound inhibited U-46619-induced bronchoconstriction in anesthetized guinea pigs (ID₅₀ = 38 µg/kg i.v.) and the 5-HT-induced increase in blood pressure in rats (ID₅₀ = 250 µg/kg i.v.). Potentially useful for the treatment of cardiovascular diseases including thrombosis and hypertension. Another related compound is:

**S-35031 [307375]^{1,2}** C31 H36 Cl N3 O5 S**SOURCE** – Servier.**REFERENCES**

1. Lavielle, G. et al. (ADIR et Cie.) *Benzenesulfonamide derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 1118610, FR 2803848.
2. Cimetière, B. et al. *Discovery of new combined 5-HT₂ and TP-receptor antagonists*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 57.
3. Simonet, S. et al. *S 35120 is a novel mixed TP- and 5-HT_{2A} receptor antagonist*. *Thromb Haemost* 2001, (Suppl.): Abst P1631.

SZ-21ScFv**305830**

Recombinant single chain Fv fragment (ScFv) of the monoclonal antibody SZ-21

ACTION – Antiplatelet agent, a single-chain antibody fragment obtained from the antiplatelet gpIIb/IIIa integrin monoclonal antibody SZ-21; it retains the binding and biological activity of the parent monoclonal antibody but does not induce thrombocytopenia. The fragment was more potent than SZ-21 in inhibiting ADP-induced platelet aggregation, with maximal inhibition at 10 µg/ml versus 20 µg/ml for SZ-21.

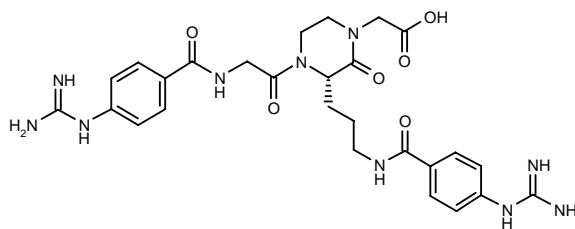
SOURCE – First Affiliated Hospital of Suzhou University, Suzhou (CN).

REFERENCES

1. An, G.Y. et al. *Constriction, expression and characterization of the ScFv fragment of the anti-platelets GPIIb/IIIa antibody SZ-21*. *Thromb Haemost* 2001, (Suppl.): Abst P1877.

TAK-024***245104**

2-[4-[2-(4-Guanidinobenzamido)acetyl]-3(S)-[3-(4-guanidinobenzamido)propyl]-2-oxopiperazin-1-yl]acetic acid



C27 H34 N10 O6; Mol wt: 594.6350

ACTION – Potent glycoprotein gpIIb/IIIa receptor antagonist proven to inhibit human platelet aggregation induced by ADP, collagen, PAF and thrombin receptor agonist peptide (TRAP), with respective IC₅₀ values of 31, 79, 30 and 91 nM. Compound inhibited ADP-induced platelet aggregation *ex vivo* in guinea pigs with an ID₅₀ value of 0.18 µg/kg/min i.v. and prolonged bleeding time 3-fold at 5.8 µg/kg/min i.v. In a balloon injury-induced carotid artery thrombosis model in guinea pigs, compound given i.v. at 1.6 µg/kg/min completely prevented thrombus formation without prolonging bleeding time. Selected as a candidate for clinical trials as a potential antithrombotic agent.

SOURCE – Takeda.

REFERENCES

1. Fukushi, H. et al. (Takeda Chemical Industries, Ltd.) *Piperazinones useful as inhibitors of platelet aggregation*. EP 0822931, JP 1997316059, US 5935963, US 6020334, WO 9633982.

2. Ohshika, M. et al. (Takeda Chemical Industries, Ltd.) *Freeze-dried preparation for pharmaceutical use*. US 5888531.

3. Takada, S. et al. (Takeda Chemical Industries, Ltd.) *Microcapsules comprising 2-piperazinone-1-acetic acid cpds*. EP 0765660.

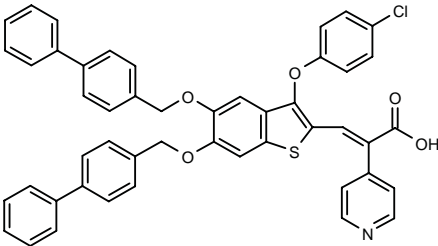
4. Kitamura, S. et al. *Potent dibasic GPIIb/IIIa antagonists with reduced prolongation of bleeding time: Synthesis and pharmacological evaluation of 2-oxopiperazine*. J Med Chem 2001, 44(15): 2438.

*Identified compound **245104** (see **244388**) Drug Data Rep 1997, 019(03): 0240.

THROMBOLYTICS

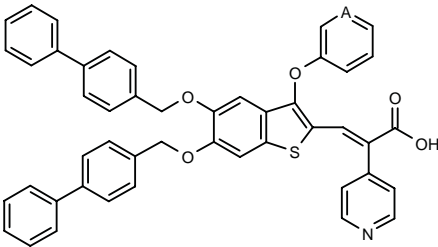
303614

3-[5,6-Bis(biphenyl-4-ylmethoxy)-3-(4-chlorophenoxy)-benzothien-2-yl]-2-(4-pyridyl)-2(E)-propenoic acid



C48 H34 Cl N O5 S; Mol wt: 772.3176

ACTION – A plasminogen activator inhibitor type 1 (PAI-1) inhibitor (IC₅₀ = 0.13 μM versus 190 μM for XR-5082), potentially useful for the treatment of fibrinolysis and thrombosis. Other exemplified compounds are:



Compound	A	Formula
303617	N	C ₄₇ H ₃₄ N ₂ O ₅ S
303618	CH	C ₄₈ H ₃₆ N ₂ O ₅ S

SOURCE – ADIR.

REFERENCES

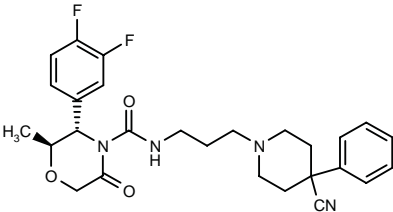
1. de Nanteuil, G. et al. (ADIR et Cie.) *Derivs. of benzothiophenes, benzofurans and indoles, method for their preparation and pharmaceutical compsns. containing them*. EP 1092716, FR 2799756, JP 2001122876.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

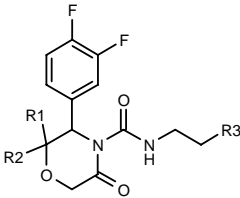
303246

(+)-trans-N-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl]-3-(3,4-difluorophenyl)-2-methyl-5-oxomorpholine-4-carboxamide



C27 H30 F2 N4 O3; Mol wt: 496.5550

ACTION – Selective human α_{1A}-adrenoceptor antagonist, as demonstrated in binding assays by K_i values of 2.6, 1456.6 and 4200.8 nM for cloned human α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors, respectively. Potentially useful for the treatment of benign prostatic hyperplasia, impotence, cardiac arrhythmia, sympathetically mediated pain and migraine, as well as for lowering intraocular pressure, for inhibiting cholesterol synthesis and for relaxing lower urinary tract tissue. A representative compound from a series of morpholinone and morpholine derivatives, wherein the following are also included:



Compound	R1=R2	R3	Formula
303247	H	4-(2-MeO-5-F-Ph)-4-Ph-1-Pip-CH2	C ₃₂ H ₃₄ F ₃ N ₃ O ₄
303248	H	4-[2-(NH2CO)-Ph]-1-Piz-CH2	C ₂₅ H ₂₉ F ₂ N ₅ O ₄
303249	H	cis-4-CN-4-Ph-cyclohexyl-NH	C ₂₆ H ₂₈ F ₂ N ₄ O ₃
303250	Me	4-(2-Pyr)-1-Pip-CH2	C ₂₆ H ₃₂ F ₂ N ₄ O ₃

SOURCE – Synaptic.

REFERENCES

1. Lagu, B. et al. (Synaptic Pharmaceutical Corp.) *Morpholinone and morpholine derivs. and uses thereof*. US 6218390.

SOURCE – Takeda.

REFERENCES

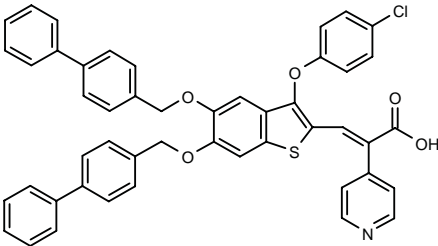
1. Fukushi, H. et al. (Takeda Chemical Industries, Ltd.) *Piperazinones useful as inhibitors of platelet aggregation*. EP 0822931, JP 1997316059, US 5935963, US 6020334, WO 9633982.
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*Identified compound **245104** (see **244388**) Drug Data Rep 1997, 019(03): 0240.

THROMBOLYTICS

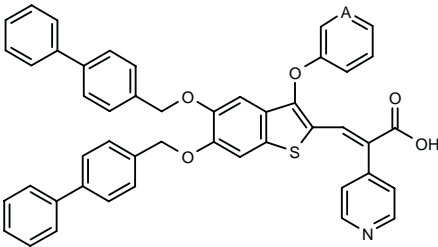
303614

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Compound	A	Formula
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303618	CH	C ₄₈ H ₃₆ N ₂ O ₅ S

SOURCE – ADIR.

REFERENCES

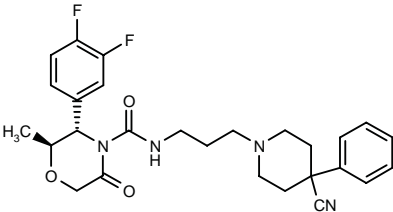
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RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

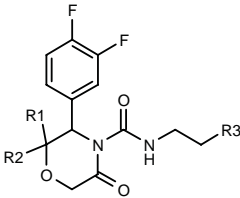
303246

(+)-*trans*-N-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl]-3-(3,4-difluorophenyl)-2-methyl-5-oxomorpholine-4-carboxamide



C27 H30 F2 N4 O3; Mol wt: 496.5550

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303248	H	4-[2-(NH2CO)-Ph]-1-Piz-CH2	C ₂₅ H ₂₉ F ₂ N ₅ O ₄
303249	H	cis-4-CN-4-Ph-cyclohexyl-NH	C ₂₆ H ₂₈ F ₂ N ₄ O ₃
303250	Me	4-(2-Pyr)-1-Pip-CH2	C ₂₆ H ₃₂ F ₂ N ₄ O ₃

SOURCE – Synaptic.

REFERENCES

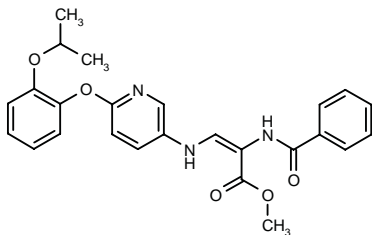
1. Lagu, B. et al. (Synaptic Pharmaceutical Corp.) *Morpholinone and morpholine derivs. and uses thereof*. US 6218390.

TREATMENT OF RENAL DISEASES

BTB-09702

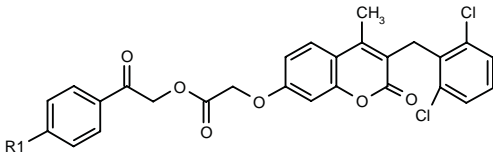
304409

2-(Benzamido)-3-[6-(2-isopropoxyphenoxy)pyridin-3-ylamino]-2-propenoic acid methyl ester

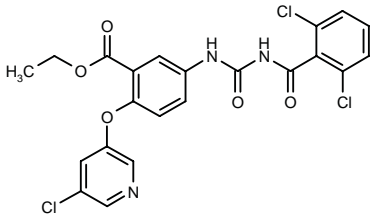


C25 H25 N3 O5; Mol wt: 447.4885

ACTION – Mesangial cell proliferation inhibitor with about 50% inhibitory activity at 0.1 μM and without cell toxicity up to 10 μM against renal proximal tubular epithelial cells. Potentially useful for the treatment of glomerular diseases including IgA nephropathy, membranoproliferative glomerulonephritis, lupus nephritis and diabetic nephropathy. Other related compounds are:



Compound	R1	Formula
RJF-01928 [304410]	Cl	C ₂₇ H ₁₉ Cl ₃ O ₆
RJF-01934 [304411]	H	C ₂₇ H ₂₀ Cl ₂ O ₆



BTB-07897 [304408]: C22 H16 Cl3 N3 O5

SOURCES – Mitsubishi Chemical; Otsuka.

REFERENCES

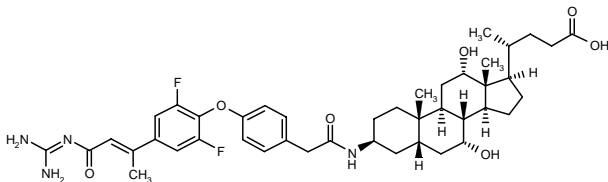
1. Kurogi, Y. et al. *Discovery of novel mesangial cell proliferation inhibitors using a three-dimensional database searching method.* J Med Chem 2001, 44(14): 2304.

GASTROINTESTINAL DRUGS

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

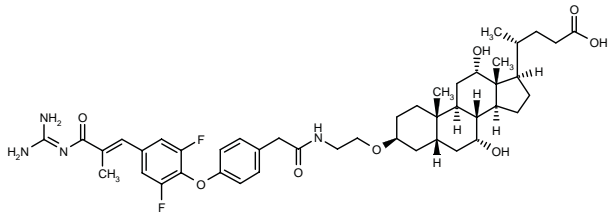
302563

(3β,5β,7α,12α)-3-[2-[4-[4-[3-Guanidino-1-methyl-3-oxo-1 (E)-propenyl]-2,6-difluorophenoxy]phenyl]acetamido]-7,12-dihydroxycholan-24-oic acid

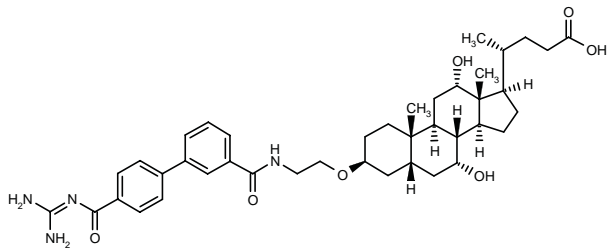


C43 H56 F2 N4 O7; Mol wt: 778.9324

ACTION – Agent for the treatment or prevention of bile stones that acts through inhibition of the Na⁺/H⁺ exchanger subtype 3 (NHE-3; the remaining activity of human NHE-3 was 10% at 30 μM). Other exemplified compounds from this series of bile acid-substituted phenyl-alkenoyl-guanidines are:



302564: C45 H60 F2 N4 O8



302565: C41 H56 N4 O7

SOURCE – Aventis Pharma.

REFERENCES

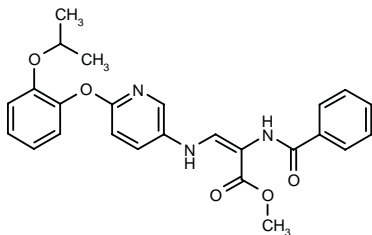
1. Kleemann, H.-W. et al. (Aventis Pharma Deutschland GmbH) *Bile acid-substd. phenyl-alkenoylguanidines, method for producing said phenyl-alkenoylguanidines, use thereof as medicaments or diagnostic reagents and medicaments containing the same.* DE 19941764, WO 0117954.

TREATMENT OF RENAL DISEASES

BTB-09702

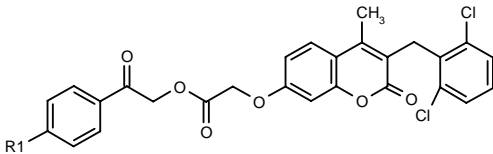
304409

2-(Benzamido)-3-[6-(2-isopropoxyphenoxy)pyridin-3-ylamino]-2-propenoic acid methyl ester

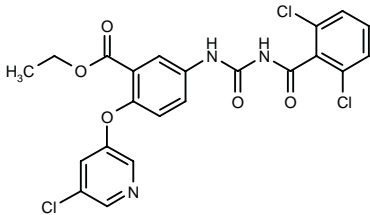


C25 H25 N3 O5; Mol wt: 447.4885

ACTION – Mesangial cell proliferation inhibitor with about 50% inhibitory activity at 0.1 μM and without cell toxicity up to 10 μM against renal proximal tubular epithelial cells. Potentially useful for the treatment of glomerular diseases including IgA nephropathy, membranoproliferative glomerulonephritis, lupus nephritis and diabetic nephropathy. Other related compounds are:



Compound	R1	Formula
RJF-01928 [304410]	Cl	C ₂₇ H ₁₉ Cl ₃ O ₆
RJF-01934 [304411]	H	C ₂₇ H ₂₀ Cl ₂ O ₆



BTB-07897 [304408]: C22 H16 Cl3 N3 O5

SOURCES – Mitsubishi Chemical; Otsuka.

REFERENCES

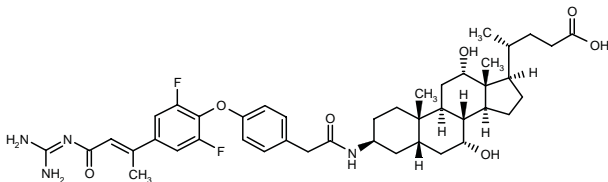
1. Kurogi, Y. et al. *Discovery of novel mesangial cell proliferation inhibitors using a three-dimensional database searching method.* J Med Chem 2001, 44(14): 2304.

GASTROINTESTINAL DRUGS

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

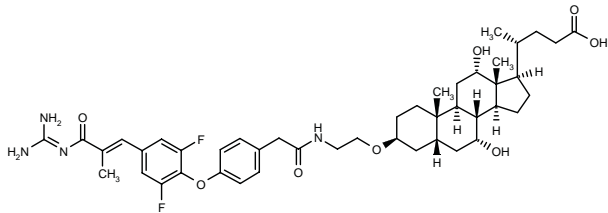
302563

(3β,5β,7α,12α)-3-[2-[4-[4-[3-Guanidino-1-methyl-3-oxo-1 (E)-propenyl]-2,6-difluorophenoxy]phenyl]acetamido]-7,12-dihydroxycholelan-24-oic acid

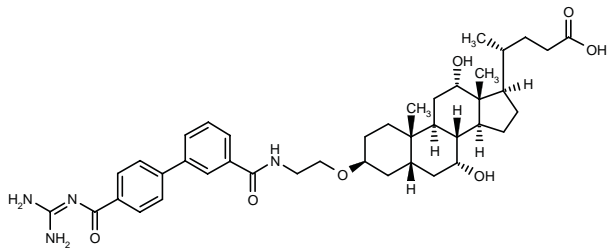


C43 H56 F2 N4 O7; Mol wt: 778.9324

ACTION – Agent for the treatment or prevention of bile stones that acts through inhibition of the Na⁺/H⁺ exchanger subtype 3 (NHE-3; the remaining activity of human NHE-3 was 10% at 30 μM). Other exemplified compounds from this series of bile acid-substituted phenyl-alkenoyl-guanidines are:



302564: C45 H60 F2 N4 O8



302565: C41 H56 N4 O7

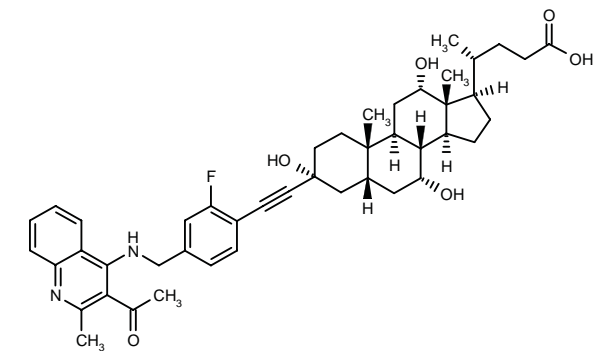
SOURCE – Aventis Pharma.

REFERENCES

1. Kleemann, H.-W. et al. (Aventis Pharma Deutschland GmbH) *Bile acid-subst. phenyl-alkenoylguanidines, method for producing said phenyl-alkenoylguanidines, use thereof as medicaments or diagnostic reagents and medicaments containing the same.* DE 19941764, WO 0117954.

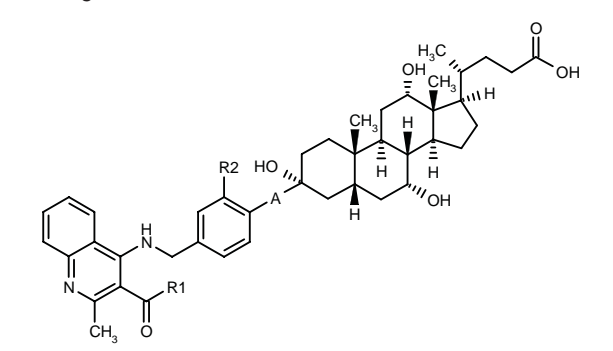
303093

(3 α ,5 β ,7 α ,12 α)-3-[2-[4-(3-Acetyl-2-methylquinolin-4-ylamino-methyl)-2-fluorophenyl]ethynyl]-3,7,12-trihydroxycholan-24-oic acid

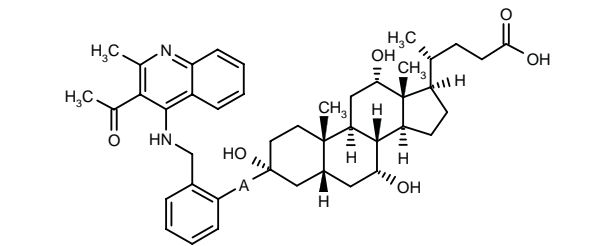


C45 H55 F N2 O6; Mol wt: 738.9355

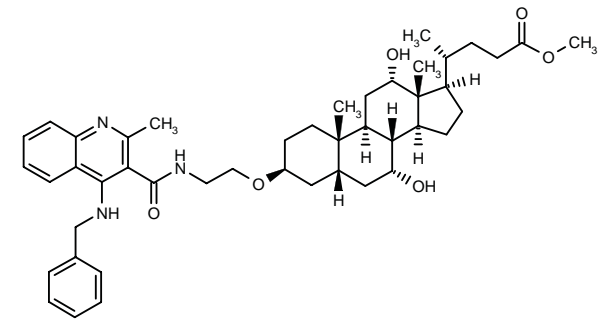
ACTION – Inhibitor of the Na⁺/H⁺ exchanger subtype 3 (NHE-3; the remaining activity of human NHE-3 was 16% at 30 μ M), potentially useful for the treatment or prevention of gallstones. Other exemplified 4-benzyl-aminoquinoline conjugates with bile acid include the following:



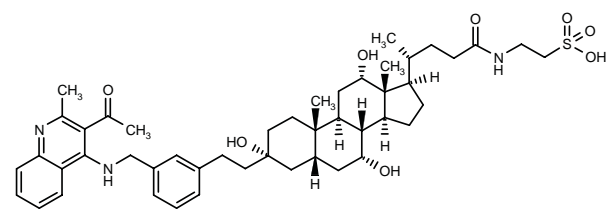
Compound	R1	R2	A	Formula
303095	Me	H	-ethynylene-	C ₄₅ H ₅₆ N ₂ O ₆
303096	Me	H	-(CH2)2-	C ₄₅ H ₆₀ N ₂ O ₆
303100	OMe	H	-ethynylene-	C ₄₅ H ₅₆ N ₂ O ₇
303108	Me	F	-(CH2)2-	C ₄₅ H ₅₉ FN ₂ O ₆
303110	Me	Cl	-ethynylene-	C ₄₅ H ₅₅ ClN ₂ O ₆



Compound	A	Formula
303103	-ethynylene-	C ₄₅ H ₅₆ N ₂ O ₆
303104	-(CH2)2-	C ₄₅ H ₆₀ N ₂ O ₆



303098: C45 H61 N3 O6



303101: C47 H65 N3 O8 S

SOURCE – Aventis Pharma.

REFERENCES

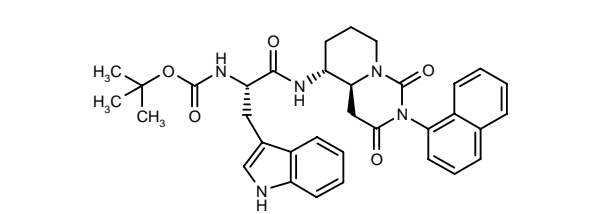
1. Hofmeister, A. et al. (Aventis Pharma Deutschland GmbH) *4-Benzylaminoquinoline conjugates with bile acid and their heteroanalogues, methods for producing the same, medicaments containing these cpds. and their use.* WO 0121642.

TREATMENT OF PANCREATIC DISORDERS

304173

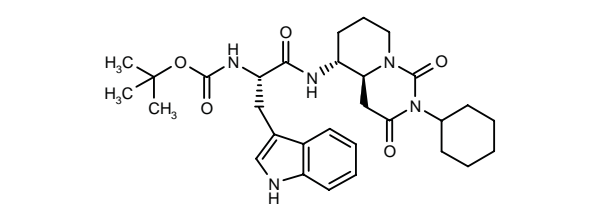
*N*²-(*tert*-Butoxycarbonyl)-*N*¹-[(4*aS*,5*R*)-2-(1-naphthyl)-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidin-5-yl]-L-tryptophanamide

N-[2-(1*H*-Indol-3-yl)-1(*S*)-[*N*-[(4*aS*,5*R*)-2-(1-naphthyl)-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidin-5-yl]carbamoyl]-ethyl]carbamic acid *tert*-butyl ester



C34 H37 N5 O5; Mol wt: 595.6963

ACTION – Potent and selective cholecystokinin CCK₁ antagonist with subnanomolar affinity for the rat pancreatic CCK₁ receptor (IC₅₀ = 0.59 nM), > 16,000-fold selectivity over CCK₂ receptors and functional antagonist activity against CCK-8-stimulated amylase secretion from pancreatic acinar cells (IC₅₀ = 0.73 nM). Potentially useful for the treatment of pancreatic disorders. Another related compound is:



304172: C30 H41 N5 O5

SOURCES – CSIC, Madrid (ES); Universidad de Navarra, Pamplona (ES).

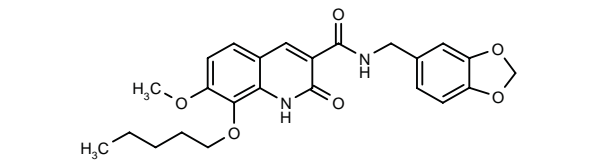
REFERENCES

1. Bartolomé-Nebreda, J.M. et al. 5-(Tryptophyl) amino-1,3-dioxoperhydropyrido[1,2-c]-pyrimidine-based potent and selective CCK1 receptor antagonists: Structure-activity relationship studies on the substituent at N2-position. J Med Chem 2001, 44(13): 2219.

JTE-907*

292443

N-(1,3-Benzodioxol-5-ylmethyl)-7-methoxy-2-oxo-8-(pentyloxy)-1,2-dihydroquinoline-3-carboxamide



C24 H26 N2 O6; Mol wt: 438.4774

ACTION – Antiinflammatory agent, a high-affinity ligand for cannabinoid CB₂ receptors with K_i values of 35.9, 1.55 and 0.38 nM for human, mouse and rat CB₂ receptors, respectively, and 66-, 684- and 2,760-fold selectivity over human, mouse and rat CB₁ receptors, respectively. Compound exhibited functional CB₂ inverse agonist activity in CHO cells expressing human and mouse CB₂ receptors. It showed dose-dependent oral antiinflammatory activity in the carrageenan-induced mouse paw edema model (ED₅₀ = 0.05 mg/kg). In a rat model of experimental acute pancreatitis, pretreatment with compound at a dose of 1 mg/kg p.o. was associated with significantly reduced pancreatic wet weight and serum IL-6 levels compared to the control group; no significant differences between groups were seen in serum TNF-α levels and ascites.

SOURCE – Japan Tobacco.

REFERENCES

1. Inaba, T. et al. (Japan Tobacco Inc.) 2-Oxoquinoline cpds. and medicinal uses thereof. JP 2000256323, WO 0040562.

2. Iwamura, H. et al. In vitro and in vivo pharmacological characterization of JTE-907, a novel selective ligand for cannabinoid CB2 receptor. J Pharmacol Exp Ther 2001, 296(2): 420.

3. Takadera, A. et al. Effects of JTE-907, a peripheral type cannabinoid receptor ligand on experimental acute pancreatitis in rats. J Jpn Pancreas Soc 2001, 16(3): Abst P-10.

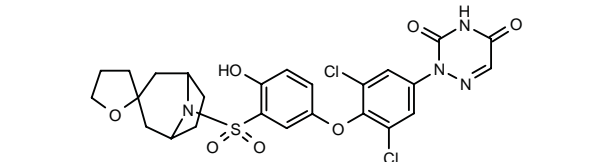
*Identified compound **292443** Drug Data Rep 2000, 022(11): 1023.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

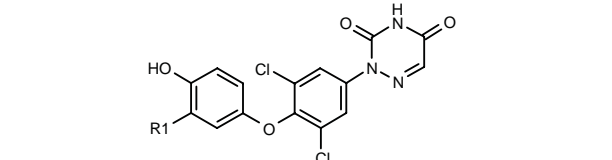
303002

2-[3,5-Dichloro-4-[4-hydroxy-3-(spiro[8-azabicyclo-[3.2.1]octane-3,2'-tetrahydrofuran]-8-ylsulfonyl)phenoxy]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione



C25 H24 Cl2 N4 O7 S; Mol wt: 595.4576

ACTION – Thyroid receptor ligand with potential for the treatment of obesity, hyperlipidemia, thyroid diseases, hypothyroidism, thyroid cancer, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, depression, osteoporosis, cardiac arrhythmias, glaucoma and congestive heart failure. Within this series of 6-azauracil derivatives, the following compounds are also included:

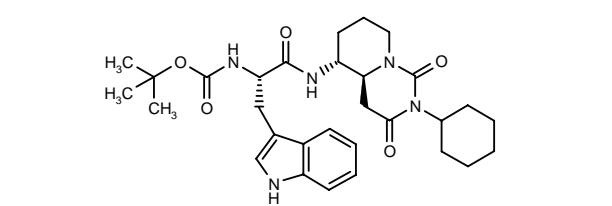


Compound	R1	Formula
303003	3,3-(Me)2-1-Pip-SO2	C ₂₂ H ₂₂ Cl ₂ N ₄ O ₆ S
303004	3-Me-3-Ph-1-Pip-SO2	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₆ S
303005	cyclohexyl-NHSO2	C ₂₁ H ₂₀ Cl ₂ N ₄ O ₆ S
303006	bicyclo[2.2.1]hept-2-yl-NHCO	C ₂₃ H ₂₀ Cl ₂ N ₄ O ₅
303007	3,3-(Me)2-1-Pip-CO	C ₂₃ H ₂₂ Cl ₂ N ₄ O ₅
303009	3-Me-3-Ph-1-Pip-CO	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₅
303010	6,6-(Me)2-bicyclo-[3.1.1]hept-2-yl-NHCO	C ₂₅ H ₂₄ Cl ₂ N ₄ O ₅
303011	3,5-(Me)2-1-Pip-CO	C ₂₃ H ₂₂ Cl ₂ N ₄ O ₅
303013	1-Pip-CO	C ₂₁ H ₁₈ Cl ₂ N ₄ O ₅

SOURCE – Pfizer.

REFERENCES

1. Dow, R.L. et al. (Pfizer Products Inc.) 6-Azauracil derivs. as thyroid receptor ligands. EP 1088819, JP 2001114768.



304172: C30 H41 N5 O5

SOURCES – CSIC, Madrid (ES); Universidad de Navarra, Pamplona (ES).

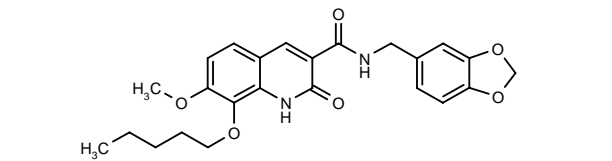
REFERENCES

1. Bartolomé-Nebreda, J.M. et al. 5-(Tryptophyl) amino-1,3-dioxoperhydropyrido[1,2-c]-pyrimidine-based potent and selective CCK1 receptor antagonists: Structure-activity relationship studies on the substituent at N2-position. J Med Chem 2001, 44(13): 2219.

JTE-907*

292443

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C24 H26 N2 O6; Mol wt: 438.4774

ACTION – Antiinflammatory agent, a high-affinity ligand for cannabinoid CB₂ receptors with K_i values of 35.9, 1.55 and 0.38 nM for human, mouse and rat CB₂ receptors, respectively, and 66-, 684- and 2,760-fold selectivity over human, mouse and rat CB₁ receptors, respectively. Compound exhibited functional CB₂ inverse agonist activity in CHO cells expressing human and mouse CB₂ receptors. It showed dose-dependent oral antiinflammatory activity in the carrageenan-induced mouse paw edema model (ED₅₀ = 0.05 mg/kg). In a rat model of experimental acute pancreatitis, pretreatment with compound at a dose of 1 mg/kg p.o. was associated with significantly reduced pancreatic wet weight and serum IL-6 levels compared to the control group; no significant differences between groups were seen in serum TNF-α levels and ascites.

SOURCE – Japan Tobacco.

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3. Takadera, A. et al. Effects of JTE-907, a peripheral type cannabinoid receptor ligand on experimental acute pancreatitis in rats. J Jpn Pancreas Soc 2001, 16(3): Abst P-10.

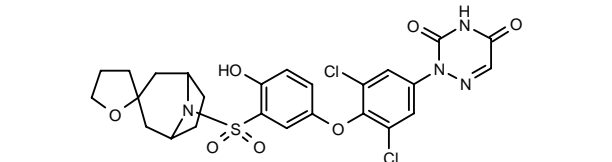
*Identified compound **292443** Drug Data Rep 2000, 022(11): 1023.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

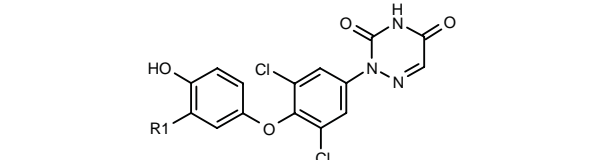
303002

2-[3,5-Dichloro-4-[4-hydroxy-3-(spiro[8-azabicyclo-[3.2.1]octane-3,2'-tetrahydrofuran]-8-ylsulfonyl)phenoxy]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione



C25 H24 Cl2 N4 O7 S; Mol wt: 595.4576

ACTION – Thyroid receptor ligand with potential for the treatment of obesity, hyperlipidemia, thyroid diseases, hypothyroidism, thyroid cancer, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, depression, osteoporosis, cardiac arrhythmias, glaucoma and congestive heart failure. Within this series of 6-azauracil derivatives, the following compounds are also included:



Compound	R1	Formula
303003	3,3-(Me)2-1-Pip-SO2	C ₂₂ H ₂₂ Cl ₂ N ₄ O ₆ S
303004	3-Me-3-Ph-1-Pip-SO2	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₆ S
303005	cyclohexyl-NHSO2	C ₂₁ H ₂₀ Cl ₂ N ₄ O ₆ S
303006	bicyclo[2.2.1]hept-2-yl-NHCO	C ₂₃ H ₂₀ Cl ₂ N ₄ O ₅
303007	3,3-(Me)2-1-Pip-CO	C ₂₃ H ₂₂ Cl ₂ N ₄ O ₅
303009	3-Me-3-Ph-1-Pip-CO	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₅
303010	6,6-(Me)2-bicyclo-[3.1.1]hept-2-yl-NHCO	C ₂₅ H ₂₄ Cl ₂ N ₄ O ₅
303011	3,5-(Me)2-1-Pip-CO	C ₂₃ H ₂₂ Cl ₂ N ₄ O ₅
303013	1-Pip-CO	C ₂₁ H ₁₈ Cl ₂ N ₄ O ₅

SOURCE – Pfizer.

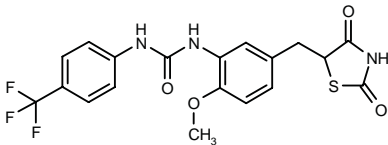
REFERENCES

1. Dow, R.L. et al. (Pfizer Products Inc.) 6-Azauracil derivs. as thyroid receptor ligands. EP 1088819, JP 2001114768.

ANTIDIABETIC DRUGS

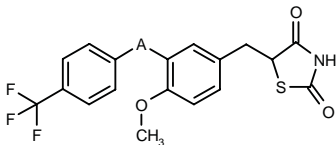
302204

N-[5-(2,4-Dioxothiazolidin-5-ylmethyl)-2-methoxyphenyl]-*N'*-[4-(trifluoromethyl)phenyl]urea



C19 H16 F3 N3 O4 S; Mol wt: 439.4124

ACTION – Human peroxisome proliferator-activated receptor (PPAR) activator proven to enhance the transcriptional activity of human PPAR α and PPAR γ in a cotransfection assay in CHO cells with EC₅₀ values of 0.55 and 0.43 μ M, respectively. Potentially useful for the treatment of diabetes and hyperlipidemia. Other exemplified compounds from this series of substituted benzylthiazolidine-2,4-dione derivatives include the following:



Compound	A	Formula
302205	-NHCOCH2-	C ₂₀ H ₁₇ F ₃ N ₂ O ₄ S
302208	-CH2CONH-	C ₂₀ H ₁₇ F ₃ N ₂ O ₄ S
302209	-CH2CH2CO-	C ₂₁ H ₁₈ F ₃ NO ₄ S

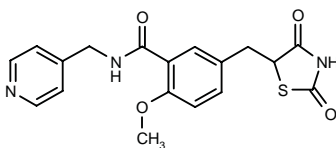
SOURCE – Kyorin.

REFERENCES

1. Miyachi, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *Substd. benzylthiazolidine-2,4-dione derivs.* WO 0114349.

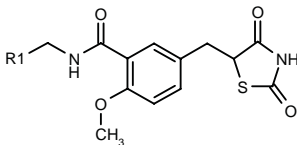
302210

5-(2,4-Dioxothiazolidin-5-ylmethyl)-2-methoxy-*N*-(pyridin-4-ylmethyl)benzamide



C18 H17 N3 O4 S; Mol wt: 371.4153

ACTION – Human peroxisome proliferator-activated receptor (PPAR) activator proven to enhance the transcriptional activity of human PPAR α and PPAR γ in a cotransfection assay in CHO cells with EC₅₀ values of 0.235 and 0.14 μ M, respectively. Potentially useful for the treatment of diabetes and hyperlipidemia. Other exemplified compounds from this series of substituted benzylthiazolidine-2,4-dione derivatives include the following:



Compound	R1	Formula
302211	2-Pyr	C ₁₈ H ₁₇ N ₃ O ₄ S
302212	3-Pyr	C ₁₈ H ₁₇ N ₃ O ₄ S
302213	cyclohexyl	C ₁₉ H ₂₄ N ₂ O ₄ S

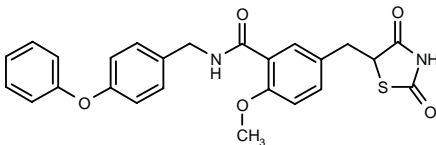
SOURCE – Kyorin.

REFERENCES

1. Fujimori, S. et al. (Kyorin Pharmaceutical Co., Ltd.) *Substd. benzylthiazolidine-2,4-dione derivs.* WO 0114350.

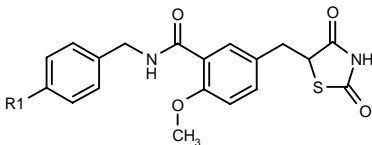
302214

5-(2,4-Dioxothiazolidin-5-ylmethyl)-2-methoxy-*N*-(4-phenoxybenzyl)benzamide



C25 H22 N2 O5 S; Mol wt: 462.5238

ACTION – Human peroxisome proliferator-activated receptor (PPAR) activator proven to enhance the transcriptional activity of human PPAR α and PPAR γ in a cotransfection assay in CHO cells with EC₅₀ values of 0.24 and 0.24 μ M, respectively. Potentially useful for the treatment of diabetes and hyperlipidemia. Other exemplified compounds from this series of substituted benzylthiazolidine-2,4-dione derivatives include the following:



Compound	R1	Formula
302215	OCH2Ph	C ₂₆ H ₂₄ N ₂ O ₅ S
302216	Ph	C ₂₅ H ₂₂ N ₂ O ₄ S

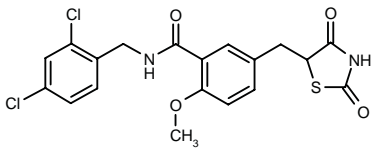
SOURCE – Kyorin.

REFERENCES

1. Miyachi, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *Substd. benzylthiazolidine-2,4-dione derivs.* WO 0114351.

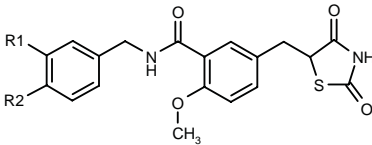
302217

N-(2,4-Dichlorobenzyl)-5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxybenzamide



C19 H16 Cl2 N2 O4 S; Mol wt: 439.3174

ACTION – Human peroxisome proliferator-activated receptor (PPAR) activator proven to enhance the transcriptional activity of human PPAR α and PPAR γ in a cotransfection assay in CHO cells with EC₅₀ values of 0.22 and 0.28 μ M, respectively. Potentially useful for the treatment of diabetes and hyperlipidemia. Other exemplified compounds from this series of substituted benzylthiazolidine-2,4-dione derivatives include the following:



Compound	R1	R2	Formula
302218	H	NO2	C ₁₉ H ₁₇ N ₃ O ₆ S
302219	H	Br	C ₁₉ H ₁₇ BrN ₂ O ₄ S
302220	H	Cl	C ₁₉ H ₁₇ ClN ₂ O ₄ S
302221	OCF3	H	C ₂₀ H ₁₇ F ₃ N ₂ O ₆ S
302222	H	OEt	C ₂₁ H ₂₂ N ₂ O ₅ S
302223	H	i-PrO	C ₂₂ H ₂₄ N ₂ O ₅ S
302224	H	OPr	C ₂₂ H ₂₄ N ₂ O ₅ S
302225	Cl	Cl	C ₁₉ H ₁₆ Cl ₂ N ₂ O ₄ S

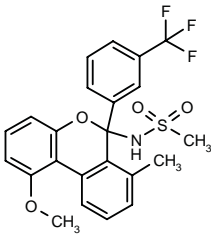
SOURCE – Kyorin.

REFERENCES

1. Nomura, M. et al. (Kyorin Pharmaceutical Co., Ltd.) *Substd. benzylthiazolidine-2,4-dione derivs.* WO 0114352.

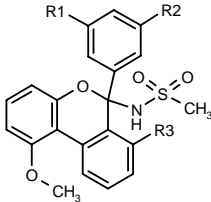
302257

N-[1-Methoxy-7-methyl-6-[3-(trifluoromethyl)phenyl]-6*H*-dibenzo[*b,d*]pyran-6-yl]methanesulfonamide



C23 H20 F3 N O4 S; Mol wt: 463.4740

ACTION – Glucocorticoid receptor (GR) antagonist with potential for the treatment of type 2 diabetes and symptoms of type 2 diabetes including hyperglycemia, inadequate glucose clearance, obesity, hyperinsulinemia, hypertriglyceridemia and high circulating glucocorticoid levels. Other specifically claimed compounds from this series of dibenzopyrans are:



Compound	R1	R2	R3	Formula
302262	H	H	Br	C ₂₁ H ₁₈ BrNO ₄ S
302263	CF3	H	Br	C ₂₂ H ₁₇ BrF ₃ NO ₄ S
302266	CF3	H	C(Me)=CH2	C ₂₅ H ₂₂ F ₃ NO ₄ S
302267	CF3	H	vinyl	C ₂₄ H ₂₀ F ₃ NO ₄ S
302268	Me	Me	Br	C ₂₃ H ₂₂ BrNO ₄ S

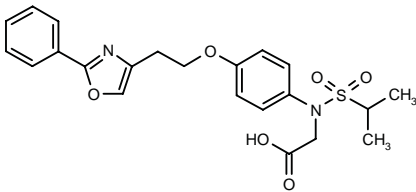
SOURCE – Abbott.

REFERENCES

1. Kym, P.R. et al. (Abbott Laboratories Inc.) *Dibenzopyrans as glucocorticoid receptor antagonists for treatment of diabetes.* WO 0116128.

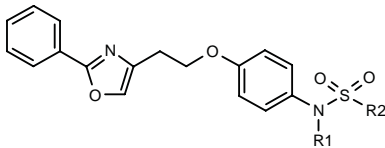
302270

2-[*N*-(Isopropylsulfonyl)-*N*-[4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl]amino]acetic acid

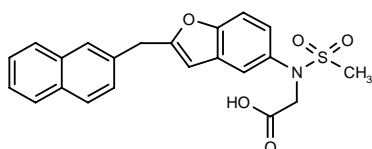


C22 H24 N2 O6 S; Mol wt: 444.5056

ACTION – Hypoglycemic and hypolipidemic agent proven active in obese diabetic viable yellow (Avy) mice, where it reduced blood glucose levels at day 14 to 53.1% of the initial value when administered orally mixed with the diet at 0.03% w/w. Other specifically claimed compounds from this series of *N,N*-arylsulfonylglycine derivatives are:



Compound	R1	R2	Formula
302271	CH2CO2H	Me	C ₂₀ H ₂₀ N ₂ O ₆ S
302274	CH2CO2H	N(Me)2	C ₂₁ H ₂₃ N ₃ O ₆ S
302276	CO2H	CH2Ph	C ₂₅ H ₂₂ N ₂ O ₆ S



302278: C₂₂ H₁₉ N O₅ S

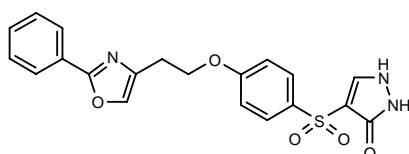
SOURCE – Lilly.

REFERENCES

1. Dominianni, S.J. (Eli Lilly and Company) *Hypoglycemic N,N-arylsulfonylglycine cpds.* WO 0116119.

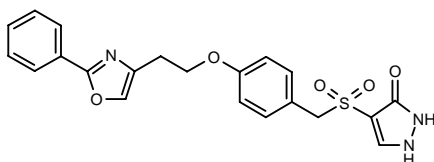
302279

4-[4-[2-(2-Phenylloxazol-4-yl)ethoxy]phenylsulfonyl]-2,3-dihydro-1H-pyrazol-3-one

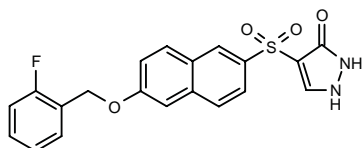


C₂₀ H₁₇ N₃ O₅ S; Mol wt: 411.4363

ACTION – Hypoglycemic and hypolipidemic agent proven active in obese diabetic viable yellow (Avy) mice, where it reduced blood glucose levels at day 14 to 32% of the initial value when administered orally mixed with the diet at 0.03% w/w. Other specifically claimed compounds from this series of sulfonyl pyrazolones and pyrazolines include the following:



302280: C₂₁ H₁₉ N₃ O₅ S



302284: C₂₀ H₁₅ F N₂ O₄ S

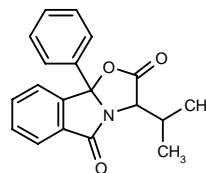
SOURCE – Lilly.

REFERENCES

1. Dominianni, S.J. (Eli Lilly and Company) *Hypoglycemic sulfonyl pyrazolones and pyrazolines.* WO 0116111.

302286

3-Isopropyl-9b-phenyl-2,3,5,9b-tetrahydrooxazolo[2,3-a]-isoindole-2,5-dione



C₁₉ H₁₇ N O₃; Mol wt: 307.3473

ACTION – Antidiabetic and antiobesity agent shown to increase plasma glucagon-like peptide-1 (GLP-1) levels in fasted rats at 30 mg/kg p.o. A representative compound from a series of isoindole derivatives.

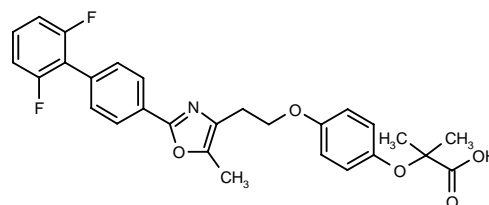
SOURCE – Banyu.

REFERENCES

1. Nagase, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel isoindole derivs.* JP 2001131175, WO 0114386.

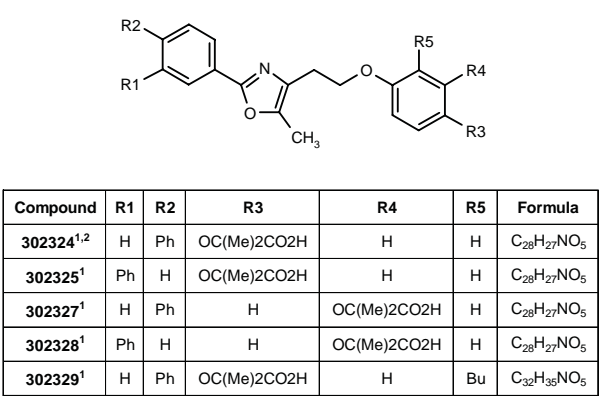
302323¹

2-[4-[2-[2-(2',6'-Difluorobiphenyl-4-yl)-5-methyloxazol-4-yl]ethoxy]phenoxy]-2-methylpropionic acid



C₂₈ H₂₅ F₂ N O₅; Mol wt: 493.5035

ACTION – Agent for the treatment of syndrome X, type 2 diabetes, hyperglycemia, hyperlipidemia, obesity, coagulopathy and cardiovascular disorders such as hypertension and atherosclerosis, a peroxisome proliferator activated receptor PPAR α and PPAR γ modulator. In binding assays, compound gave IC₅₀ values of 155 and 457 nM, respectively, for human PPAR α and PPAR γ receptors, being more potent than troglitazone (IC₅₀ = 94.5 μ M and 1180 nM, respectively) and fenofibric acid (IC₅₀ = 68 and 125 μ M, respectively). In addition, it produced 67.5 and 66% decreases in triglyceride and HDL cholesterol levels in human ApoA1 transgenic mice at 30 mg/kg/day p.o. x 7 days, and it was found to completely normalize blood glucose levels in diabetic *db/db* mice at 30 mg/kg/day p.o. x 7 days. Other exemplified compounds from this series of biaryl-oxa(thia)zole derivatives include the following:



SOURCES – Ligand; Lilly.

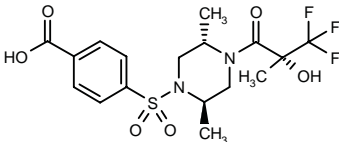
REFERENCES

1. Brooks, D.A. et al. (Eli Lilly and Company; Ligand Pharmaceuticals, Inc.) *Biaryl-oxa(thia)zole derivs. and their use as PPARs modulators*. WO 0116120.

2. Brooks, D.A. et al. *Design and synthesis of 2-methyl-2-{4-[2-(5-methyl-2-aryloxazol-4-yl)ethoxy]phenoxy}propionic acids: A new class of dual PPARα/γ agonists*. J Med Chem 2001, 44(13): 2061.

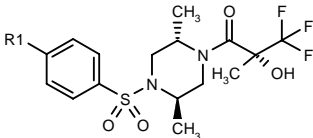
302524

4-[2(*R*),5(*S*)-Dimethyl-4-[3,3,3-trifluoro-2(*R*)-hydroxy-2-methylpropionyl]piperazin-1-ylsulfonl]benzoic acid



C17 H21 F3 N2 O6 S; Mol wt: 438.4209

ACTION – Pyruvate dehydrogenase (PDH) activity enhancer, potentially useful for the treatment of diseases related to reduced PDH such as diabetes mellitus, peripheral vascular disease and myocardial ischemia. Other specifically claimed amides are:



Compound	R1	Formula
302525	CON(Me)2	C ₁₉ H ₂₆ F ₃ N ₃ O ₅ S
302526	F	C ₁₆ H ₂₀ F ₄ N ₂ O ₅ S
302528	NHCH2CH2OH	C ₁₈ H ₂₆ F ₃ N ₃ O ₅ S
302529	CN	C ₁₇ H ₂₀ F ₃ N ₃ O ₄ S
302530	OMe	C ₁₇ H ₂₃ F ₃ N ₂ O ₅ S

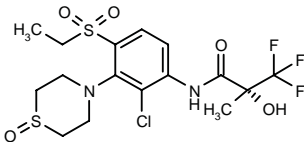
SOURCE – AstraZeneca.

REFERENCES

1. Butlin, R.J. et al. (AstraZeneca AB;AstraZeneca plc) *Amides as inhibitors for pyruvate dehydrogenase*. WO 0117942.

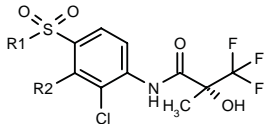
302531

N-[2-Chloro-4-(ethylsulfonyl)-3-(1-oxidothiophorolin-4-yl)phenyl]-3,3,3-trifluoro-2(*R*)-hydroxy-2-methylpropion- amide



C16 H20 Cl F3 N2 O5 S2; Mol wt: 476.9220

ACTION – Pyruvate dehydrogenase (PDH) activity enhancer, potentially useful for the treatment of diseases related to reduced PDH such as diabetes mellitus, peripheral vascular disease and myocardial ischemia. Other specifically claimed substituted *N*-phenyl 2-hydroxy-3-methyl-3,3,3-trifluoropropanamide derivatives are:



Compound	R1	R2	Formula
302532	i-Pr	1-oxido-4-thiomorpholinyl	C ₁₇ H ₂₂ ClF ₃ N ₂ O ₅ S ₂
302533	Me	1,1-dioxo-4-thiomorpholinyl	C ₁₅ H ₁₈ ClF ₃ N ₂ O ₆ S ₂
302534	Et	1,1-dioxo-4-thiomorpholinyl	C ₁₆ H ₂₀ ClF ₃ N ₂ O ₆ S ₂
302535	i-Pr	1,1-dioxo-4-thiomorpholinyl	C ₁₇ H ₂₂ ClF ₃ N ₂ O ₆ S ₂
302536	Et	SMe	C ₁₃ H ₁₅ ClF ₃ NO ₄ S ₂
302537	Me	SMe	C ₁₂ H ₁₃ ClF ₃ NO ₄ S ₂
302550	Et	4-Ac-1-Piz	C ₁₈ H ₂₃ ClF ₃ N ₃ O ₅ S
302553	Me	4-Ac-1-Piz	C ₁₇ H ₂₁ ClF ₃ N ₃ O ₅ S
302554	Me	4-morpholinyl	C ₁₅ H ₁₈ ClF ₃ N ₂ O ₅ S
302555	i-Pr	4-Ac-1-Piz	C ₁₉ H ₂₅ ClF ₃ N ₃ O ₅ S
302557	i-Pr	4-morpholinyl	C ₁₇ H ₂₂ ClF ₃ N ₂ O ₅ S

SOURCE – AstraZeneca.

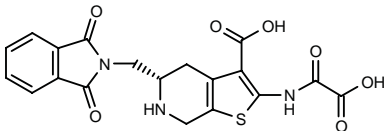
REFERENCES

1. Butlin, R.J. et al. (AstraZeneca AB;AstraZeneca plc) *Substd. N-phenyl-2-hydroxy-2-methyl-3,3,3-trifluoropropanamide derivs. which elevate pyruvate dehydrogenase activity*. WO 0117956.

302559

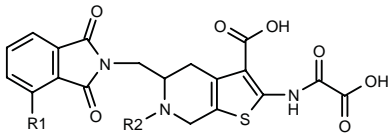
2-(Oxaloamino)-5(*S*)-(phthalimidomethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid

N-[3-Carboxy-5(*S*)-(phthalimidomethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]oxamic acid



C19 H15 N3 O7 S; Mol wt: 429.4075

ACTION – Agent for the treatment of autoimmune diseases, acute and chronic inflammation, osteoporosis, cancer, type 1 and type 2 diabetes and obesity, a selective inhibitor of protein-tyrosine-phosphatase 1B (PTP1B), T-cell PTP (TC-PTP) and other PTPs having an aspartic acid at position 48. *In vitro*, compound gave a K_i value of 0.07 μ M against PTP1B, compared to K_i values of 1000 and 8 μ M, respectively, against PTP α and PTP β , both having Asn instead of Asp at position 48. Other exemplified compounds include the following:



Compound	R1	R2	Formula
302560	H	CO2Et	C ₂₂ H ₁₉ N ₃ O ₉ S
302561	H	H	C ₁₉ H ₁₅ N ₃ O ₇ S
302562	OH	H	C ₁₉ H ₁₅ N ₃ O ₈ S

SOURCES – Novo Nordisk; Ontogen.

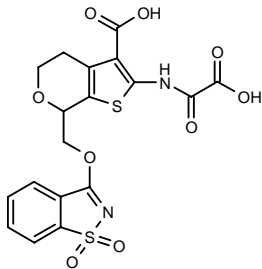
REFERENCES

1. Andersen, H.S. et al. (Novo Nordisk A/S; Ontogen Corp.) *Method of inhibiting protein tyrosine phosphatase 1B and/or T-cell protein tyrosine phosphatase and/or other PTPases with an ASP residue at position 48.* WO 0117516.

302892

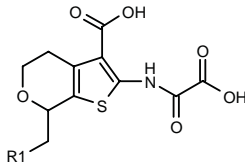
7-(1,1-Dioxido-1,2-benzisothiazol-3-yloxymethyl)-2-(oxaloamino)-5,7-dihydro-4*H*-thieno[2,3-*c*]pyran-3-carboxylic acid

N-[3-Carboxy-7-(1,1-dioxido-1,2-benzisothiazol-3-yloxymethyl)-5,7-dihydro-4*H*-thieno[2,3-*c*]pyran-2-yl]-oxamic acid

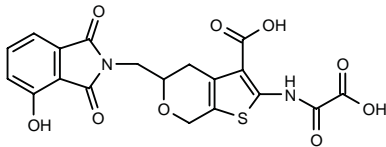


C18 H14 N2 O9 S2; Mol wt: 466.4456

ACTION – An inhibitor of protein-tyrosine-phosphatases (PTPases) such as PTP1B (K_i = 0.8 μ M), CD45, SHP-1, SHP-2, PTP α , LAR and HePTP, potentially useful for the treatment of a broad range of diseases such as type 1 and type 2 diabetes, impaired glucose tolerance, insulin resistance, obesity, autoimmune diseases, coagulation disorders, allergic diseases, osteoporosis, cancer, psoriasis, neurological disorders and infectious diseases. Other exemplified bicyclic compounds include the following:



Compound	R1	Formula
302902	5-MeO-1,3-dioxo-2,3-dihydro-2-isindolyl	C ₂₀ H ₁₆ N ₂ O ₉ S
302904	5,7-dioxo-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isindol-6-yl	C ₂₀ H ₁₄ N ₂ O ₁₀ S
302906	5-(4-imidazolyl-CH=)-2,4-dioxo-3-thiazolidinyl	C ₁₈ H ₁₄ N ₄ O ₉ S ₂
302907	1,1,3-trioxo-2,3-dihydro-1H-1,2-benzisothiazol-2-yl	C ₁₈ H ₁₄ N ₂ O ₉ S ₂
302908	1,1,3-trioxo-5-Ph-2,3-dihydro-2-isothiazolyl	C ₂₀ H ₁₆ N ₂ O ₉ S ₂
302909	1,1-dioxo-5-Ph-3-isothiazolyl-O	C ₂₀ H ₁₆ N ₂ O ₉ S ₂
302910	1,3-dioxo-2,3-dihydro-1,2-benzisothiazol-2-yl	C ₁₈ H ₁₄ N ₂ O ₈ S ₂



302901: C19 H14 N2 O9 S

SOURCES – Novo Nordisk; Ontogen.

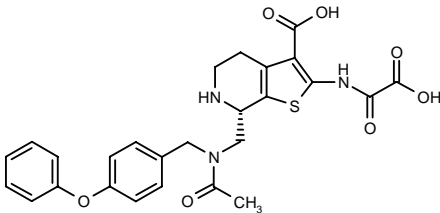
REFERENCES

1. Andersen, H.S. et al. (Novo Nordisk A/S; Ontogen Corp.) *Modulators of protein tyrosine phosphatases (PTPases).* WO 0119831.

302912

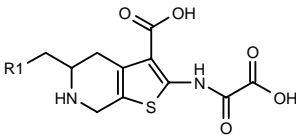
7(*S*)-[*N*-Acetyl-*N*-(4-phenoxybenzyl)aminomethyl]-2-(oxaloamino)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid

N-[7(*S*)-[*N*-Acetyl-*N*-(4-phenoxybenzyl)aminomethyl]-3-carboxy-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]-oxamic acid

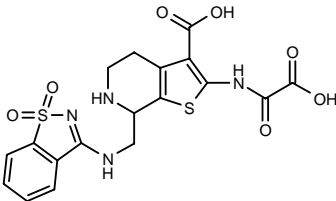


C26 H25 N3 O7 S; Mol wt: 523.5635

ACTION – An inhibitor of protein-tyrosine-phosphatases (PTPases) such as PTP1B (K_i = 220 nM), CD45, SHP-1, SHP-2, PTP α , LAR and HePTP, potentially useful for the treatment of a broad range of diseases such as type 1 and type 2 diabetes, impaired glucose tolerance, insulin resistance, obesity, autoimmune diseases, coagulation disorders, allergic diseases, osteoporosis, cancer, psoriasis, neurological disorders and infectious diseases. Other exemplified bicyclic compounds include the following:



Compound	R1	Formula
302914	4-OH-1-oxo-2,3-dihydro-2-isoindolyl	C ₁₉ H ₁₇ N ₃ O ₇ S
302916	1,1-dioxo-1,2-benzisothiazol-3-yl-NH	C ₁₈ H ₁₆ N ₄ O ₇ S ₂
302919	7-MeO-1-oxo-2,3-dihydro-2-isoindolyl	C ₂₀ H ₁₉ N ₃ O ₇ S
302921	3-indolyl-COCONH	C ₂₁ H ₁₈ N ₄ O ₇ S
302923	6-MeO-4-CO2Me-1-oxo-2,3-dihydro-2-isoindolyl	C ₂₂ H ₂₁ N ₃ O ₉ S



302918: C18 H16 N4 O7 S2

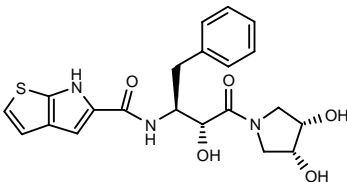
SOURCES – Novo Nordisk; Ontogen.

REFERENCES

1. Andersen, H.S. et al. (Novo Nordisk A/S; Ontogen Corp.) *Modulators of protein tyrosine phosphatases (PTPases)*. WO 0119830.

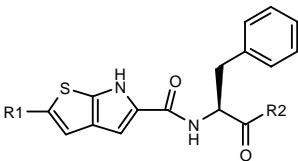
303015

N-[1(S)-Benzyl-3-[3(R),4(S)-dihydroxypyrrolidin-1-yl]-2(R)-hydroxy-3-oxopropyl]-6H-thieno[2,3-b]pyrrole-5-carboxamide

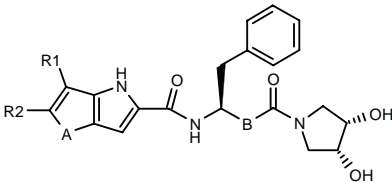


C21 H23 N3 O5 S; Mol wt: 429.4947

ACTION – Agent for the treatment of diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hypertension, hyperlipidemia, atherosclerosis and tissue ischemia, an inhibitor of glycogen phosphorylase. Other compounds from this series of bicyclic pyrrolyl amide derivatives include the following:



Compound	R1	R2	Formula
303016	Br	3(R),4(S)-(OH)2-1-pyrrolidinyl	C ₂₀ H ₂₀ BrN ₃ O ₄ S
303018	Cl	N(Me)2	C ₁₈ H ₁₈ ClN ₃ O ₂ S
303019	ethynyl	3-OH-1-azetidiny	C ₂₁ H ₁₉ N ₃ O ₃ S



Compound	R1	R2	A	B	Formula
303017	H	Br	S	-(R)-CH(OH)-	C ₂₁ H ₂₂ BrN ₃ O ₅ S
303020	H	Cl	O	-(R)-CH(OH)-	C ₂₁ H ₂₂ ClN ₃ O ₆
303022	Br	H	S	-(R)-CH(OH)-	C ₂₁ H ₂₂ BrN ₃ O ₅ S
303023	H	CN	S	bond	C ₂₁ H ₂₀ N ₄ O ₄ S
303024	H	SMe	S	bond	C ₂₁ H ₂₃ N ₃ O ₄ S ₂

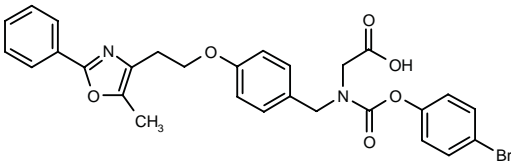
SOURCE – Pfizer.

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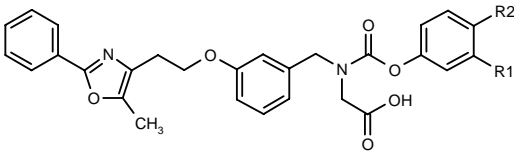
303113

2-[N-(4-Bromophenoxycarbonyl)-N-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]amino]acetic acid

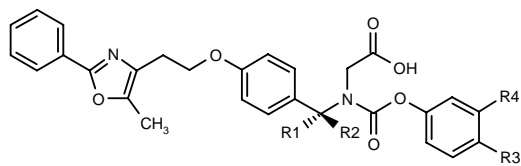


C28 H25 Br N2 O6; Mol wt: 565.4175

ACTION – Agent that lowers blood glucose, triglyceride, insulin and nonesterified fatty acid levels, potentially useful as an antidiabetic, hypolipidemic and antiobesity agent, particularly for the treatment of type 2 diabetes mellitus. Other compounds from this series of oxa- and thiazole derivatives are:



Compound	R1	R2	Formula
303115	H	Me	C ₂₉ H ₂₈ N ₂ O ₆
303117	OMe	H	C ₂₉ H ₂₈ N ₂ O ₇
303118	Br	H	C ₂₈ H ₂₅ BrN ₂ O ₆
303119	OEt	H	C ₃₀ H ₃₀ N ₂ O ₇



Compound	R1	R2	R3	R4	Formula
303121	H	H	Me	H	C ₂₉ H ₂₈ N ₂ O ₆
303122	H	H	OMe	H	C ₂₉ H ₂₈ N ₂ O ₇
303124	Me	H	OMe	H	C ₃₀ H ₃₀ N ₂ O ₇
303125	H	Me	OMe	H	C ₃₀ H ₃₀ N ₂ O ₇
303127	H	H	H	OMe	C ₂₉ H ₂₈ N ₂ O ₇

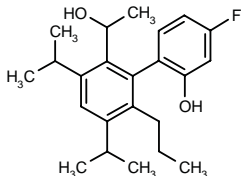
SOURCE – Bristol-Myers Squibb.

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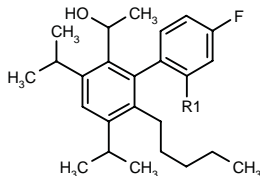
303229

4-Fluoro-2'-(1-hydroxyethyl)-3',5'-diisopropyl-6'-propylbiphenyl-2-ol



C23 H31 F O2; Mol wt: 358.4939

ACTION – Glucagon receptor antagonist (IC₅₀ = 0.005 μM against [¹²⁵I]-glucagon binding to human glucagon receptors expressed in CHO cells), potentially useful for the treatment of glucagon-mediated conditions such as diabetes, impaired glucose tolerance, insulin resistance, obesity, hyperlipidemia, acute pancreatitis, cardiovascular disorders and gastrointestinal disorders. Other exemplified compounds from this series of substituted biphenyls include the following:



Compound	R1	Formula
303233	H	C ₂₅ H ₃₅ FO
303234	OH	C ₂₅ H ₃₅ FO ₂

SOURCE – Bayer.

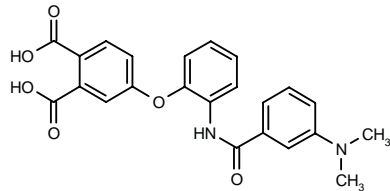
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303375

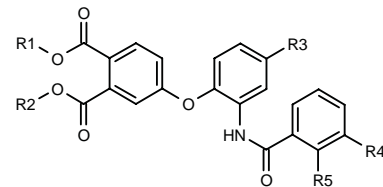
4-[2-[3-(Dimethylamino)benzamido]phenoxy]phthalic acid

4-[2-[3-(Dimethylamino)benzamido]phenoxy]benzene-1,2-dicarboxylic acid



C23 H20 N2 O6; Mol wt: 420.4190

ACTION – Agent for the treatment or prevention of diabetes, particularly type 2 diabetes, as well as obesity and for appetite regulation, that is reported to inhibit glycogen phosphorylase and liver glucose production. Other specifically claimed compounds from this series of aromatic derivatives include the following:



Compound	R1=R2	R3	R4	R5	Formula
303376	Me	H	I	H	C ₂₃ H ₁₈ INO ₆
303378	H	H	F	F	C ₂₁ H ₁₃ F ₂ NO ₆
303379	H	NH2	NO2	H	C ₂₁ H ₁₅ N ₃ O ₈
303380	Me	H	NO2	H	C ₂₃ H ₁₈ N ₂ O ₈
303381	H	CO2Me	NO2	H	C ₂₃ H ₁₆ N ₂ O ₁₀
303382	Me	CN	NO2	H	C ₂₄ H ₁₇ N ₃ O ₈
303383	H	3-NO2-PhCONH	NO2	H	C ₂₈ H ₁₈ N ₄ O ₁₁
303384	Me	H	OMe	H	C ₂₄ H ₂₁ NO ₇

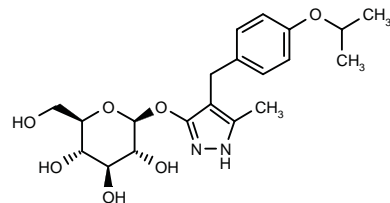
SOURCE – Novo Nordisk.

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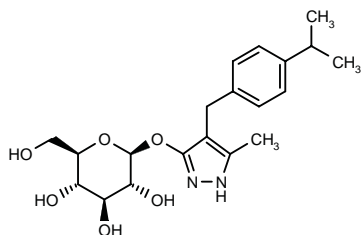
303558

1-O-[4-(4-Isopropoxybenzyl)-5-methyl-1H-pyrazol-3-yl]-β-D-glucopyranose



C20 H28 N2 O7; Mol wt: 408.4482

ACTION – Agent for the treatment or prevention of diabetes, diabetic complications and obesity, an inhibitor of the human sodium-dependent glucose transporter type 2 (SGLT2; IC_{50} = 181 nM in COS-7 cells transiently transfected with hSGLT2). *In vivo*, compound was shown to dose-dependently promote urinary glucose excretion in rats when given at 0.1-10 mg/kg i.v. No mortality was observed following administration of 600 mg/kg s.c. to mice. Another compound from this series of glucopyranosyloxypyrazole derivatives is:



303559: C20 H28 N2 O6

SOURCE – Kissei.

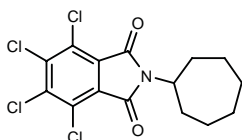
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304740

4,5,6,7-Tetrachloro-2-cycloheptyl-1*H*-isoindole-1,3(2*H*)-dione

3,4,5,6-Tetrachloro-*N*-cycloheptylphthalimide



C15 H13 Cl4 N O2; Mol wt: 381.0847

ACTION – α -Glucosidase inhibitor (IC_{50} = 1 μ M) potentially useful for the treatment of various diseases including diabetes, obesity, AIDS, hepatitis B and hepatitis C.

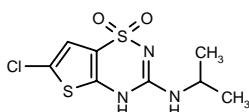
SOURCE – University of Tokyo, Tokyo (JP).

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305185

6-Chloro-*N*-isopropyl-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-amine 1,1-dioxide



C8 H10 Cl N3 O2 S2; Mol wt: 279.7710

ACTION – Diazoxide analogue, an ATP-sensitive potassium channel (K_{ATP}) opener proven to selectively activate the human pancreatic SUR1/Kir6.2 channel (EC_{50} = 1.1 μ M) but not the heart and skeletal muscle SUR2A/Kir6.2 channel or the smooth muscle SUR2B/Kir6.2 channel expressed in *Xenopus* oocytes. Compound also inhibited glucose-mediated insulin release from isolated mouse pancreatic islets (IC_{50} = 0.06 μ M). When compared with the parent diazoxide, compound was about 30-fold more potent in activating SUR1/Kir6.2 channels but showed similar or less activity in relaxing rat thoracic aorta and guinea pig urinary bladder *in vitro*. Potentially useful for the treatment or prevention of diabetes.

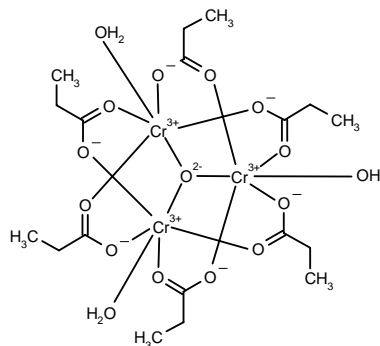
SOURCE – Novo Nordisk.

REFERENCES

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305202

Triaqua- μ_3 -oxohexakis[μ -(propanoato- $\kappa O:\kappa O'$)]-trichromium(1+)



C18 H36 Cr3 O16; Mol wt: 664.4544

ACTION – Biomimetic for the chromium-binding oligopeptide chromodulin, proven to lower serum insulin, triglyceride and total cholesterol levels in healthy rats and in Zucker obese rats but not in streptozotocin-diabetic rats. Compound did not affect plasma glucose levels, suggesting that it may act as an insulin sensitizer. Potentially useful for the treatment of type 2 diabetes.

SOURCE – University of Alabama, Tuscaloosa, AL (US).

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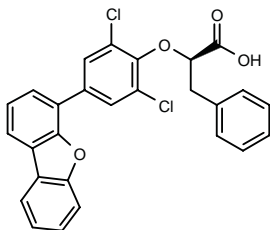
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A-321842

305192

2(*R*)-[2,6-Dichloro-4-(dibenzo[*b,d*]furan-4-yl)phenoxy]-3-phenylpropionic acid



C27 H18 Cl2 O4; Mol wt: 477.3412

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor (IC_{50} = 18 μ M) proven to lower both plasma glucose and insulin levels in *ob/ob* mice at 100 mg/kg p.o. for 5 days. The compound showed excellent pharmacokinetic properties with an oral availability of 96.6% and a half-life of 14.5 h. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Abbott.

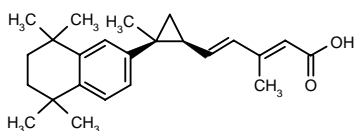
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1. Pei, Z. et al. (2*R*)-2-(2',6'-Dichloro-4'-dibenzo(*b,d*)furan-4''-ylphenoxy)-3-phenylpropionic acid (A-321842) as a protein tyrosine phosphatase 1B (PTP1B) inhibitor with anti-diabetic effects in *ob/ob* mice. Diabetes 2001, 50(Suppl. 2): Abst 1524-P.

AGN-194204¹⁻³

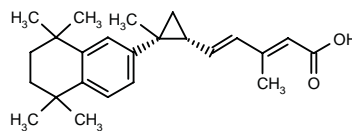
304433

3-Methyl-5-[(1*S*,2*S*)-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]-2(*E*),4(*E*)-pentadienoic acid



C24 H32 O2

ACTION – Retinoid X receptor (RXR) ligand with higher affinity for RXR α than for RXR β and RXR γ receptors (K_d = 0.4, 3.6 and 3.8 nM, respectively) and no detectable affinity for retinoic acid receptors (RAR). Compound exhibited functional agonist activity, as measured in a transactivation assay in CV-1 cells transfected with RXR α , RXR β and RXR γ receptors (EC_{50} = 0.5, 0.8 and 0.08 nM, respectively). *In vivo*, it exhibited potent hypoglycemic activity in diabetic *db/db* mice, giving respective 37 and 53% reductions in serum glucose at doses of 0.4 and 2 mg/kg/day p.o. Potentially useful for the treatment of diabetes. Its antipode **AGN-194277** is also an effective RXR agonist but shows lower affinity.



AGN-194277 [304404]:^{1,3} C24 H32 O2

SOURCE – Allergan.

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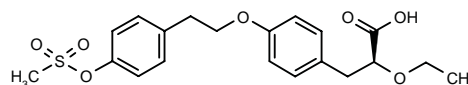
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AZ-242

259635

2(*S*)-Ethoxy-3-[4-[2-[4-(methylsulfonyloxy)phenyl]ethoxy]-phenyl]propionic acid

AR-H039242XX



C20 H24 O7 S; Mol wt: 408.4686

ACTION – Dual peroxisome proliferator-activated receptor PPAR α and PPAR γ activator with respective IC_{50} values of 1.0 and 0.2 μ M for binding affinity and respective EC_{50} values of 2.8 and 0.32 μ M for PPAR α and PPAR γ activation in cell-based reporter gene assays. Compound induced adipocyte differentiation *in vitro* (EC_{50} = 0.1 μ M) in 3T3-L1 cells. When administered to *ob/ob* mice (0.01-100 μ mol/kg/day p.o. for 8 days), dose-dependent reductions in elevated plasma glucose, insulin and triglyceride levels were seen, with no increase in body weight. In this model, compound was approximately 2-fold more potent than the racemate, 7-fold more potent than rosiglitazone and 250-fold more potent than pioglitazone. Other studies in obese Zucker *fa/fa* rats showed that compound after 1 (1 μ mol/kg/day p.o.) or 3 (3 μ mol/kg/day p.o.) weeks of treatment produced a complete reversal of whole-body insulin resistance, apparently due to enhanced hepatic and peripheral insulin actions, particularly restoration of the ability of insulin to reduce fatty acid availability. In a genetic model of insulin resistance using double transgenic human apoB/CETP (cholesterol ester transfer protein) mice, compound improved both diet-induced insulin resistance and the associated dyslipidemia, with a superior profile to the selective PPAR γ agonist rosiglitazone and the selective PPAR α agonist Wy-14643. In a nongenetic model of insulin resistance using Wistar rats fed a high-fat diet, AZ-242 (1 μ mol/kg/day p.o. for 7 days) improved insulin sensitivity and reduced plasma triglycerides, and significantly increased fatty acid uptake into white adipocyte tissue, while having no effect on uptake into red gastrocnemius muscle or liver. Compound is undergoing phase II clinical trials. Potentially useful for the treatment of insulin resistance-related glucose and lipid abnormalities associated with type 2 diabetes and the insulin resistance syndrome.

SOURCE – AstraZeneca.

REFERENCES

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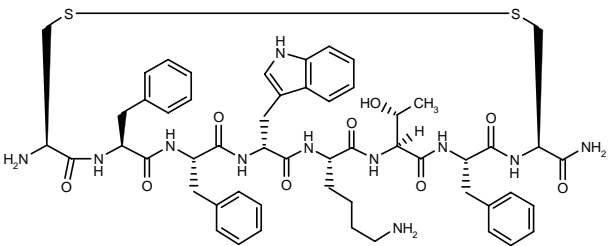
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BIM-23268

285904

L-Cysteiny-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinamide cyclic-(1-8)-disulfide

BIM-23268D



C54 H67 N11 O9 S2; Mol wt: 1078.3230

ACTION – Somatostatin analogue with high affinity for the human sst₅ receptor (IC₅₀ = 0.42 nM) over human sst₁, sst₂, sst₃ and sst₄ receptors (IC₅₀ = 12, 28, 5.5 and 36 nM, respectively), proven to significantly reduce glucose-induced insulin release and amylin production in perfused rat pancreas (68 and 46% reduction, respectively, at 10 μ M). Acute and subchronic experiments in obese animals indicated that compound enhances insulin sensitivity. In insulin-resistant obese *fa/fa* Zucker rats, compound strongly reduced insulin production when given at a dose of 3 mg/kg b.i.d. s.c. for 7 days; this effect was associated with a reduction in body weight, plasma triglycerides and glycerol levels, but no significant effect on blood glucose levels or food intake. A similar profile was seen in *ob/ob* mice. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Biomeasure.

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BP1-01

305228

L-Cysteinyl-L-arginyl-L-alanyl-glycyl-L-prolyl-L-leucyl-L-glutaminy-L-tryptophyl-L-leucyl-L-cysteinyl-L-glutamyl-L-lysyl-L-tyrosyl-L-phenylalanine

C79 H116 N20 O19 S2; Mol wt: 1714.0380

ACTION – Insulin sensitizer, a synthetic peptide found to inhibit insulin-like growth factor-I (IGF-I) binding to IGF-binding protein-1 (IGFBP-1) and enhance IGF-I activity in human hepatoma Hep G2 cells. Moreover, this peptide enhanced glycogen synthesis in response to insulin in Hep G2 cells. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Genentech.

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INSULIN CHAIN B (9-23) PEPTIDE

305047

Insulin(human) chain B (9-23) peptide

L-Seryl-L-histidyl-L-leucyl-L-valyl-L-glutamyl-L-alanyl-L-leucyl-L-tyrosyl-L-leucyl-L-valyl-L-cysteinyl-glycyl-L-glutamyl-L-arginyl-glycine

C72 H116 N20 O22 S; Mol wt: 1645.8920

ACTION – Immunodominant insulin epitope able to induce insulin autoantibodies and prevent diabetes in BALB/c and nonobese diabetic (NOD) mice that spontaneously develop autoimmune insulinitis and diabetes. Potentially useful for the treatment of type 1 diabetes.

SOURCE – University of Colorado, Boulder, CO (US).

REFERENCES

1. Wegmann, D.R. (University of Colorado) *Epitope for prevention of type I diabetes.* US 5594100.

2. Abiru, N. et al. *Peptide and major histocompatibility complex-specific breaking of humoral tolerance to native insulin with the B9-23 peptide in diabetes-prone and normal mice.* Diabetes 2001, 50(6): 1274.

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4. Daniel, D. and Wegmann, D.R. *Protection of nonobese diabetic mice from diabetes by intranasal or subcutaneous administration of insulin peptide B-(9-23).* Proc Natl Acad Sci USA 1996, 93(2): 956.

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7. Wegmann, D.R. et al. *Analysis of the spontaneous T cell response to insulin in NOD mice.* J Autoimmun 1994, 7(6): 833.

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NBI-6024

273845

[16B-L-Alanine,19B-L-alanine]insulin(human) chain B (9-23) peptide

H-L-Ser-L-His-L-Leu-L-Val-L-Glu-L-Ala-L-Leu-L-Ala-L-Leu-L-Val-L-Ala-Gly-L-Glu-L-Arg-Gly-OH

C66 H112 N20 O21; Mol wt: 1521.7300

ACTION – Antidiabetic agent for the treatment of type 1 diabetes, an altered peptide ligand (APL) proven to generate Th2-like lymphocytes in nonobese diabetic mice (NOD), and thereby prevent β -islet cell destruction and hyperglycemia. Results from a multicenter, randomized, dose-escalation study in type 1 insulin-dependent diabetic patients indicated that compound is well tolerated when administered as a single s.c. dose up to 10 mg or multiple doses up to 5 mg.

SOURCES – Neurocrine Biosciences; Taisho.

REFERENCES

1. Gaur, A. et al. (Neurocrine Biosciences Inc.) *Methods for treatment of diabetes using peptide analogues of insulin.* US 6197926, WO 9942482.

2. Distiller, L.A. et al. *Multiple-dose safety and tolerability of NBI-6024: A new altered peptide ligand for type 1 diabetes mellitus.* Diabetes 2001, 50(Suppl. 2): Abst 1808-PO.

3. Scholtz, H. et al. *Single dose safety and tolerability of NBI-6024: A new altered peptide ligand for type 1 diabetes mellitus.* Diabetes 2001, 50(Suppl. 2): Abst 522-P.

4. *Altered peptide ligand agreement between Neurocrine Biosciences and Taisho expanded.* DailyDrugNews.com (Daily Essentials) 2000, Dec 13.

5. *Neurocrine and Taisho complete final agreement; preliminary phase I data for NBI-6024 promising.* DailyDrugNews.com (Daily Essentials) 2000, July 25.

6. *Neurocrine Biosciences expands clinical development efforts during Q2.* DailyDrugNews.com (Daily Essentials) 2001, Aug 29.

7. *Neurocrine Biosciences licenses antidiabetic compound to Taisho.* DailyDrugNews.com (Daily Essentials) 2000, Jan 11.

8. *Neurocrine Biosciences reports clinical development progress.* DailyDrugNews.com (Daily Essentials) 2001, May 8.

9. *Neurocrine Biosciences to begin U.S. trials with altered peptide ligand for type 1 diabetes .* DailyDrugNews.com (Daily Essentials) 2000, Nov 10.

10. *Neurocrine discontinues development of DHEA; to advance other programs.* DailyDrugNews.com (Daily Essentials) 1999, March 5.

11. *Neurocrine's APL compound enters phase I trial for IDDM.* DailyDrugNews.com (Daily Essentials) 1999, March 18.

12. *Phase I/II program for NBI-6024 expanded; pivotal phase IIb trial to commence later this year.* DailyDrugNews.com (Daily Essentials) 2001, Feb 23.

O-346***256308****[[N^ε-(19-Carboxynonadecanoyl)]Lys^{B29},des-Ala^{B30}]-insulin(human)**

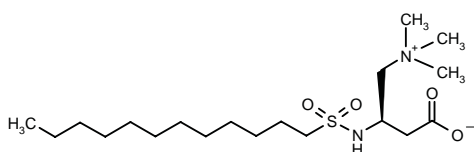
ACTION – Fatty acid acylated insulin analogue with very high binding affinity for albumin; the plasma compartment appears to act as a storage compartment from which it is slowly released to insulin-sensitive tissues. In anesthetized dogs, compound at a dose of 15 U/kg i.v. showed a very slow onset of activity but its effect on glucose disposal was maintained over at least 8 h.

SOURCE – Novo Nordisk.

REFERENCES

1. Schäffer, L. and Balschmidt, P. (Novo Nordisk A/S) *Insulin derivs. and their use*. JP 2000504732, WO 9731022.
2. Hansen, L.B. (Novo Nordisk A/S) *Selective acylation method*. US 5905140, WO 9802460.
3. Ellmerer, M. et al. *Extremely prolonged action of the dicarboxylic acid acylated insulin analog O346 after intravenous injection in dogs*. 37th Annu Meet Eur Assoc Study Diabetes (Sept 9-13, Glasgow) 2001, Abst 800.
4. Ellmerer, M. et al. *Extremely prolonged action of the dicarboxylic acid acylated insulin analog O346 after intravenous injection in dogs*. Diabetes 2001, 50(Suppl. 2): Abst 445-P.

*Identified compound **256308** (see **255090**) Drug Data Rep 1998, 020(01): 0051.

ST-1420**293877****3(R)-(Dodecylsulfonamido)-4-(trimethylammonium)-butyrate**

C19 H40 N2 O4 S; Mol wt: 392.6010

ACTION – Aminocarnitine derivative, a selective inhibitor of liver mitochondrial carnitine palmitoyltransferase (CPT I) (IC₅₀ = 0.7 and 3.4 μM against liver and heart CPT I, respectively). *In vivo*, compound reduced plasma β-hydroxybutyrate levels (ED₅₀ = 20 mg/kg p.o.) in fasted rats and serum glucose levels in *db/db* mice (100 mg/kg/day p.o. x 30). Potentially useful for the treatment of type 2 diabetes.

SOURCE – Sigma-Tau.

REFERENCES

1. Giannessi, F. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Cpds. having reversible inhibiting activity of carnitine palmitoyl-transferase*. EP 1077925, WO 9959957.
2. Arduini, A. et al. *Reversible carnitine palmitoyltransferase inhibitors with antidiabetic activity. 2. Aminocarnitine derivatives*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PC-13.
3. Giannessi, F. et al. *Reversible carnitine palmitoyltransferase inhibitors with broad chemical diversity as potential antidiabetic agents*. J Med Chem 2001, 44(15): 2383.

[Aib^{8,35}]hGLP-1(1-36)NH₂**305458****H-His-Asp-Glu-Phe-Glu-Arg-His-2-aminoisobutyryl-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-2-aminoisobutyryl-Arg-NH₂**

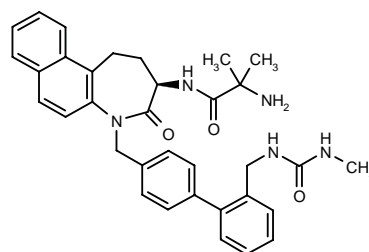
C187 H279 N51 O57; Mol wt: 4153.5610

ACTION – Human glucagon-like peptide-1 (GLP-1) analogue with a significantly improved plasma half-life and efficacy in stimulating insulin release and lowering blood glucose in diabetic animals compared to native GLP-1. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Biomeasure.

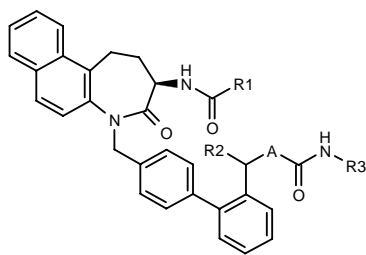
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1. Dong, J.Z. et al. *Glucagon-like peptide-1 analogs with significantly improved in vivo activity*. 17th Am Peptide Symp (June 9-14, San Diego) 2001, Abst P413.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS**302401****2-Amino-2-methyl-N-[5-[2'-(3-methylureidomethyl)-biphenyl-4-ylmethyl]-4-oxo-2,3,4,5-tetrahydro-1H-naphtho[2,1-b]azepin-3(R)-yl]propionamide**

C34 H37 N5 O3; Mol wt: 563.6983

ACTION – Growth hormone (GH) release-promoting agent for the treatment of disorders characterized by a deficiency of GH secretion such as short stature in GH-deficient children, and for the treatment of disorders which are improved by the anabolic effects of GH, particularly osteoporosis. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	A	Formula
302403	(R)-CH2C(Me)2NH-CH2CH(OH)Me	H	Me	NH	C ₃₈ H ₄₅ N ₅ O ₄
302405	(R)-CH2C(Me)2NH-CH2CH(OH)Me	H	H	NH	C ₃₇ H ₄₃ N ₅ O ₄
302406	C(Me)2NH2	H	Et	NH	C ₃₅ H ₃₉ N ₅ O ₃
302408	CH2C(Me)2NH2	H	CH2CH2OH	NH	C ₃₆ H ₄₁ N ₅ O ₄
302410	C(Me)2NH2	Me	Me	NH	C ₃₅ H ₃₉ N ₅ O ₃
302411	CH2C(Me)2NH2	H	Me	O	C ₃₅ H ₃₈ N ₄ O ₄
302412	(S)-CH2C(Me)2NH-CH2CH(OH)CH2OH	H	Me	O	C ₃₈ H ₄₄ N ₄ O ₆

SOURCE – Merck & Co.

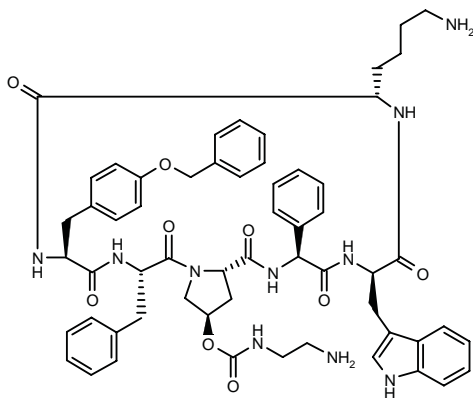
REFERENCES

1. Devita, R.J. and Wyvratt, M.J. (Merck & Co., Inc.) *Naphtho-fused lactams promote release of growth hormone*. US 6211174.

SOM-230

305198

Cyclo[[4(R)-[N-(2-aminoethyl)carbamoyloxy]]-L-prolyl-L-phenylglycyl-D-tryptophyl-L-lysyl-(4-O- benzyl)-L-tyrosyl-L-phenylalanyl]



C58 H66 N10 O9; Mol wt: 1047.2200

ACTION – Cyclohexapeptide somatostatin analogue with 30-40-fold higher affinity for sst₁ and sst₅ receptors compared with octreotide. This new analogue is also more potent than octreotide as an inhibitor of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis in animals. Potentially useful for the treatment of disorders related to hypersecretion of GH.

SOURCE – Novartis.

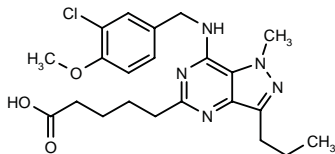
REFERENCES

1. Lewis, I. et al. *Rational approach to stable, universal somatostatin analogues with superior therapeutic potential*. 17th Am Peptide Symp (June 9-14, San Diego) 2001, Abst L68.

TREATMENT OF MALE SEXUAL DYSFUNCTION

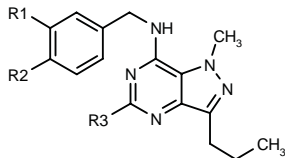
302386

5-[7-(3-Chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]pentanoic acid



C22 H28 Cl N5 O3; Mol wt: 445.9482

ACTION – Agent for the treatment of cardiovascular disorders, particularly cardiac insufficiency, and erectile dysfunction with phosphodiesterase type 5 (PDE 5)-inhibitory activity. Other specifically claimed compounds from this series of pyrazolo[4,3-*d*]pyrimidines are:



Compound	R1	R2	R3	Formula
302387	Cl	OMe	4-CO2H-Ph	C ₂₄ H ₂₄ ClN ₅ O ₃
302389	-OCH2O-		(CH2)3CO2H	C ₂₁ H ₂₅ N ₅ O ₄
302391	H	H	(CH2)4CO2H	C ₂₁ H ₂₇ N ₅ O ₂

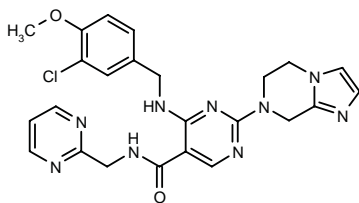
SOURCE – Merck KGaA.

REFERENCES

1. Jonas, R. et al. (Merck Patent GmbH) *Pyrazolo[4,3-*d*]pyrimidines*. DE 19942474, WO 0118004.

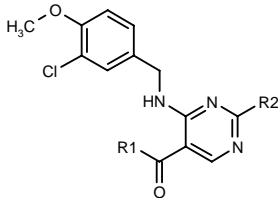
303130

4-(3-Chloro-4-methoxybenzylamino)-*N*-(pyrimidin-2-ylmethyl)-2-(5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-7-yl)pyrimidine-5-carboxamide



C24 H24 Cl N9 O2; Mol wt: 505.9676

ACTION – A selective inhibitor of phosphodiesterase type 5 (PDE5) that may be useful for the treatment of erectile dysfunction, as well as hypertension, angina pectoris, myocardial infarction, chronic and acute heart failure, prostatic hypertrophy, asthma, diarrhea, etc. Other exemplified aromatic nitrogen-containing six-membered ring compounds are:



Compound	R1	R2	Formula
303131	trans-4-OH-cyclohexyl-NH	4-CHO-1-Piz	C ₂₄ H ₃₁ ClN ₆ O ₄
303132	3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl-NH	2(S)-(HOCH2)-1-pyrrolidinyl	C ₂₆ H ₂₇ ClN ₆ O ₅
303133	2-pyrimidinyl-CH2NH	4-Me-3-oxo-1-Piz	C ₂₃ H ₂₅ ClN ₈ O ₃
303134	2-pyrimidinyl-CH2NH	3-(CH2OH)-1-Pip	C ₂₄ H ₂₈ ClN ₇ O ₃
303135	2-Pyr-CH2CH2NH	2(S)-(HOCH2)-1-pyrrolidinyl	C ₂₅ H ₂₉ ClN ₆ O ₃
303136	1-(CNCH2)-4-Pip-NH	2(S)-(HOCH2)-1-pyrrolidinyl	C ₂₅ H ₃₂ ClN ₇ O ₃
303137	CH2PO(OMe)2	2(S)-(HOCH2)-1-pyrrolidinyl	C ₂₁ H ₂₈ ClN ₄ O ₆ P
303138	4,6-(Me)2-2-pyrimidinyl-NH	2(S)-(HOCH2)-1-pyrrolidinyl	C ₂₄ H ₂₈ ClN ₇ O ₃

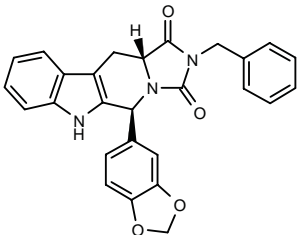
SOURCE – Tanabe Seiyaku.

REFERENCES

1. Yamada, K. et al. (Tanabe Seiyaku Co., Ltd.) *Aromatic nitrogenous six-membered ring cpds.* WO 0119802.

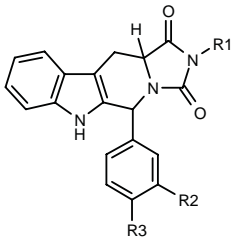
303241

cis-5-(1,3-Benzodioxol-5-yl)-2-benzyl-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3-dione



C27 H21 N3 O4; Mol wt: 451.4799

ACTION – Agent for the treatment of cardiovascular disorders, renal failure, atherosclerosis, peripheral vascular disorders, inflammatory disorders, stroke, asthma, erectile dysfunction and gut motility disorders, a potent and selective inhibitor of cGMP phosphodiesterase type 5 (PDE5; IC₅₀ < 10 nM using recombinant human enzyme), proven to stimulate the accumulation of cGMP in rat aortic smooth muscle cells (EC₅₀ = 0.3 μM). Significant hypotensive activity was observed in conscious spontaneously hypertensive rats at a dose of 5 mg/kg p.o. Other tetracyclic compounds include the following:



Compound	R1	R2	R3	Isomer	Formula
303243	Bu	H	OMe	trans	C ₂₄ H ₂₅ N ₃ O ₃
303244	cyclohexyl	H	OMe	trans	C ₂₆ H ₂₇ N ₃ O ₃
303245	CH2Ph	-OCH2O-		5R,11aR	C ₂₇ H ₂₁ N ₃ O ₄

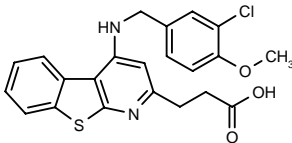
SOURCE – Icos.

REFERENCES

1. Daugan, A.C.-M. and LaBaudiniere, R.F. (Icos Corp.) *Treatment method using a cGMP-specific PDE inhibitor.* US 6218400.

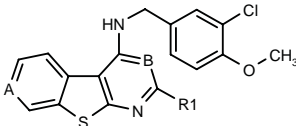
303196

3-[4-(3-Chloro-4-methoxybenzylamino)[1]benzothieno[2,3-*b*]pyridin-2-yl]propionic acid

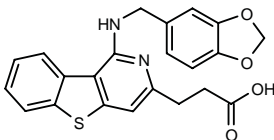


C22 H19 Cl N2 O3 S; Mol wt: 426.9221

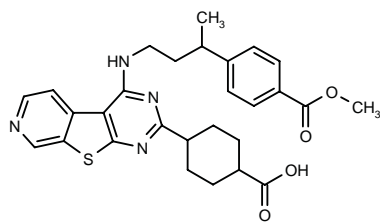
ACTION – A selective inhibitor of phosphodiesterase type 5 (PDE5) that may be useful for the treatment of erectile dysfunction, as well as angina pectoris, hypertension, pulmonary hypertension, congestive heart failure, peripheral vascular disease, bronchitis, asthma, glaucoma, irritable bowel syndrome, tumors, renal insufficiency and liver cirrhosis. Other specifically claimed amides are:



Compound	R1	A	B	Formula
303201	4-(NH2SO2)-cyclohexyl	CH	CH	C ₂₅ H ₂₆ ClN ₃ O ₃ S ₂
303202	4-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-cyclohexyl	CH	CH	C ₂₇ H ₂₅ ClN ₄ O ₂ S ₂
303203	4-(CO2HCH2)-PhCH2	CH	N	C ₂₇ H ₂₂ ClN ₃ O ₃ S
303204	6-(CO2HCH2CH2)-2-Pyr-CH2	CH	N	C ₂₇ H ₂₃ ClN ₄ O ₃ S
303205	4-(CO2HCH2CH2)-1-Pip-CH2	CH	N	C ₂₇ H ₂₉ ClN ₄ O ₃ S
303206	4-(5-tetrazolyl)-CH2CH2)-1-Piz-CH2CH2	CH	N	C ₂₇ H ₃₀ ClN ₉ OS
303207	4-(CO2HCH2CH2)-cyclohexyl-CH2CH2	N	N	C ₂₈ H ₃₁ ClN ₄ O ₃ S



303200: C22 H18 N2 O4 S



303208: C₂₈ H₃₀ N₄ O₄ S

SOURCE – Merck KGaA.

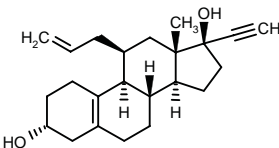
REFERENCES

1. Eiermann, V. and Jonas, R. (Merck Patent GmbH) *Amine derivs.* DE 19944604, WO 0121620.

TREATMENT OF GYNECOLOGICAL DISORDERS

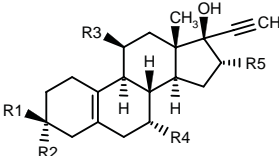
302442

(3 α ,11 β ,17 β)-11-Allyl-17-ethynylestr-5(10)-ene-3,17-diol

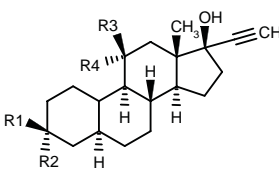


C₂₃ H₃₂ O₂; Mol wt: 340.5038

ACTION – Estrogenic compound with selective affinity for the estrogen ER α receptor, as demonstrated in binding assays in recombinant CHO cells stably transfected with the human ER α or ER β receptor and in transactivation assays in CHO cells cotransfected with the rat oxytocin promoter, the luciferase reporter gene and the human ER α or ER β receptor. Potentially useful for the treatment and prevention of estrogen-related disorders such as menopausal complaints and osteoporosis, as well as Alzheimer’s disease, breast cancer, benign prostatic hypertrophy and cardiovascular disorders, and as a contraceptive. Other exemplified compounds from this series of nonaromatic estrogenic steroids with a hydrocarbon substituent at position 11 of the steroid skeleton include the following:



Compound	R1	R2	R3	R4	R5	Formula
302443	OH	H	allyl	H	Me	C ₂₄ H ₃₄ O ₂
302448	H	OH	allyl-CH2	H	H	C ₂₄ H ₃₄ O ₂
302450	OH	H	allyl-CH2	H	H	C ₂₄ H ₃₄ O ₂
302451	OH	H	CH2CH2F	Me	H	C ₂₃ H ₃₃ FO ₂
302452	H	OH	CH2CH2F	Me	H	C ₂₃ H ₃₃ FO ₂
302453	OH	H	Me	Me	Me	C ₂₃ H ₃₄ O ₂
302454	H	OH	Me	Me	Me	C ₂₃ H ₃₄ O ₂



Compound	R1	R2	R3	R4	Formula
302444	OH	H	H	CHF2	C ₂₁ H ₃₀ F ₂ O ₂
302445	OH	H	H	CH2CH2F	C ₂₂ H ₃₃ FO ₂
302446	H	OH	H	CH2CH2F	C ₂₂ H ₃₃ FO ₂
302455	H	OH	-CH2-		C ₂₃ H ₃₄ O ₂

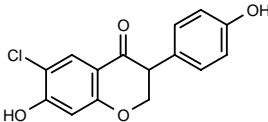
SOURCE – Akzo Nobel.

REFERENCES

1. Loozen, H.J.J. et al. (Akzo Nobel N.V.) *Non-aromatic estrogenic steroids with a hydrocarbon substituent in position 11.* WO 0118027.

302484

6-Chloro-7-hydroxy-3-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one



C₁₅ H₁₁ Cl O₄; Mol wt: 290.7009

ACTION – Agent that competitively binds to estrogen ER α and ER β receptors, claimed for the treatment or prevention of a broad range of conditions including menopausal syndrome, osteoporosis, premenstrual syndrome, Raynaud’s syndrome, coronary artery spasm, migraine, hypertension, benign prostatic hypertrophy, cancer, atherosclerosis, Alzheimer’s disease, inflammatory diseases, acne, baldness, psoriasis, myocardial infarction and stroke. A representative compound from a series of isoflavone derivatives.

SOURCE – Novogen.

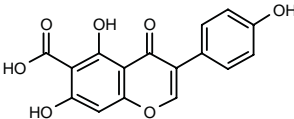
REFERENCES

1. Heaton, A. et al. (Novogen Ltd.) *Compsns. and therapeutic methods involving isoflavones and analogues thereof.* WO 0117986.

6-CARBOXYGENISTEIN

305200

5,7-Dihydroxy-3-(4-hydroxyphenyl)-4-oxo-4H-1-benzopyran-6-carboxylic acid



C₁₆ H₁₀ O₇; Mol wt: 314.2480

ACTION – Selective estrogen receptor modulator (SERM), a carboxy derivative of genistein with high affinity for ER β receptors (IC₅₀ = 0.5 μ M) and minimal affinity for ER α receptors. Compound, like genistein, stimulated DNA synthesis and creatine kinase (CK) activity in human umbilical smooth muscle cells and human endothelial cells, and CK activity in immature or ovariectomized rat tissues. Unlike genistein, this derivative did not inhibit protein tyrosine kinase in a cell-based assay and did not increase CK activity in the uterus. Moreover, compound inhibited estrogen-induced CK stimulation in rat tissues and estrogen-induced smooth muscle cell proliferation. Compound was 5-10-fold more potent than raloxifene in blocking the CK response to estrogen in rat tissues derived from both immature and ovariectomized rats. Potentially useful for the treatment of osteoporosis and other postmenopausal symptoms, as well as for the prevention of breast and endometrial cancer.

SOURCES – Tel-Aviv Sourasky Medical Center, Tel-Aviv (IL); Tel Aviv University, Tel Aviv (IL); University of Texas Medical Branch at Galveston, Galveston, TX (US); Weizmann Institute of Science, Rehovot (IL).

REFERENCES

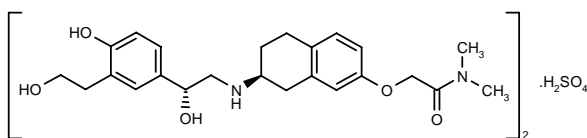
1. Somjen, D. et al. 6-Carboxy genistein: A novel selective estrogen receptor modulator (SERM) with unique effects on the vasculature, bone and uterus. 83rd Annu Meet Endocr Soc (June 20-23, Denver) 2001, Abst P2-75.

UTERINE STIMULANTS AND TOCOLYTICS

KUR-1246

295058

(-)-2-[7(S)-[2(R)-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethylamino]-5,6,7,8-tetrahydronaphthalen-2-yloxy]-N,N-dimethylacetamide sulfate (2:1)



C48 H64 N4 O10 . H2 O4 S; Mol wt: 955.1294

ACTION – Uterine relaxant, a selective β_2 -adrenoceptor agonist (pK_i = 7.59, 5.75 and 4.75 for β_2 -, β_1 - and β_3 -adrenoceptors, respectively) proven to strongly inhibit spontaneous and oxytocin-induced contractions of pregnant myometrium of rats (pD₂ = 9.04 and 8.53, respectively) and rabbits (pD₂ = 8.71 and 8.60, respectively). Compound also inhibited PGF_{2 α} - and KCl-induced contractions of myometrium in pregnant rats (pD₂ = 7.3 and 8.51, respectively). *In vivo*, it reduced the frequency of spontaneous uterine activity with an ED₃₀ value of 0.13 μ g/kg/min, and was about 6- and 400-fold more potent, respectively, than terbutaline and ritodrine. Unlike ritodrine and terbutaline, compound induced only a weak positive chronotropic effect. Potentially useful for the treatment of preterm labor in humans.

SOURCES – Kissei; Teikoku Hormone.

REFERENCES

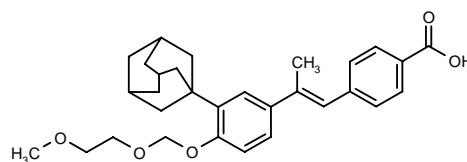
1. Kitazawa, M. et al. (Kissei Pharmaceutical Co., Ltd.) 3,4-Disubst. phenylethanolaminotetralincarboxamide derivs. EP 0882704, US 6133266, WO 9730023.
2. Kobayashi, M. et al. Action of KUR-1246, a novel therapeutic agent for threatened premature delivery, on uterine contraction, cardiohemodynamics and fetus in domestic rabbits in later stages. Acta Obstet Gynaecol Jpn 2001, 53(2): Abst P-179.
3. Kobayashi, M. et al. Characterization of KUR-1246 as a highly selective β_2 -adrenoceptor agonist for a uterine relaxant. Int J Gynecol Obstet 2000, 70(Suppl. 1): Abst P2.15.24.
4. Kobayashi, M. et al. Pharmacological characterization of KUR-1246, a selective uterine relaxant. J Pharmacol Exp Ther 2001, 297(2): 666.
5. Yanagi, T. et al. The practical synthesis of a uterine relaxant, bis (2-[[2S)-2-(((2R)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)-phenyl]ethyl]amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy)-N,N-dimethylacetamide) sulfate (KUR-1246). Chem Pharm Bull 2001, 49(8): 1018.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

302913

4-[2-[3-(1-Adamantyl)-4-(2-methoxyethoxymethoxy)phenyl]-1(E)-propenyl]benzoic acid



C30 H36 O5; Mol wt: 476.6094

ACTION – Agent with cell differentiation- and cell proliferation-modulating activity and potential in the topical or systemic treatment of dermatological conditions related to keratinization disorders or having an inflammatory and/or immunoallergic component, benign or malignant dermal or epidermal proliferative disorders, connective tissue degenerative disorders, cicatrization disorders and corneopathies, for combatting skin aging, as well as for the treatment of inflammatory disorders, cancerous and precancerous conditions, alopecia and cardiovascular disorders. *In vitro*, compound was shown to antagonize CD-2043-induced secretion of plasminogen activator in mouse embryonic teratocarcinoma F9 cells with an IC₅₀ value of 9 nM. Other compounds from this series of stilbene derivatives comprising an adamantyl group include the following:

ACTION – Selective estrogen receptor modulator (SERM), a carboxy derivative of genistein with high affinity for ER β receptors (IC₅₀ = 0.5 μ M) and minimal affinity for ER α receptors. Compound, like genistein, stimulated DNA synthesis and creatine kinase (CK) activity in human umbilical smooth muscle cells and human endothelial cells, and CK activity in immature or ovariectomized rat tissues. Unlike genistein, this derivative did not inhibit protein tyrosine kinase in a cell-based assay and did not increase CK activity in the uterus. Moreover, compound inhibited estrogen-induced CK stimulation in rat tissues and estrogen-induced smooth muscle cell proliferation. Compound was 5-10-fold more potent than raloxifene in blocking the CK response to estrogen in rat tissues derived from both immature and ovariectomized rats. Potentially useful for the treatment of osteoporosis and other postmenopausal symptoms, as well as for the prevention of breast and endometrial cancer.

SOURCES – Tel-Aviv Sourasky Medical Center, Tel-Aviv (IL); Tel Aviv University, Tel Aviv (IL); University of Texas Medical Branch at Galveston, Galveston, TX (US); Weizmann Institute of Science, Rehovot (IL).

REFERENCES

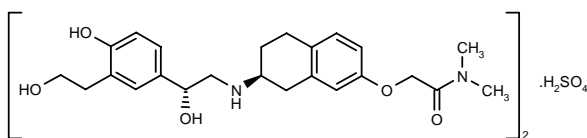
1. Somjen, D. et al. 6-Carboxy genistein: A novel selective estrogen receptor modulator (SERM) with unique effects on the vasculature, bone and uterus. 83rd Annu Meet Endocr Soc (June 20-23, Denver) 2001, Abst P2-75.

UTERINE STIMULANTS AND TOCOLYTICS

KUR-1246

295058

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C48 H64 N4 O10 . H2 O4 S; Mol wt: 955.1294

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SOURCES – Kissei; Teikoku Hormone.

REFERENCES

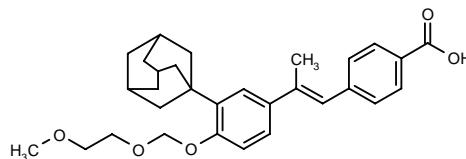
1. Kitazawa, M. et al. (Kissei Pharmaceutical Co., Ltd.) 3,4-Disubst. phenylethanolaminotetralincarboxamide derivs. EP 0882704, US 6133266, WO 9730023.
2. Kobayashi, M. et al. Action of KUR-1246, a novel therapeutic agent for threatened premature delivery, on uterine contraction, cardiohemodynamics and fetus in domestic rabbits in later stages. Acta Obstet Gynaecol Jpn 2001, 53(2): Abst P-179.
3. Kobayashi, M. et al. Characterization of KUR-1246 as a highly selective β_2 -adrenoceptor agonist for a uterine relaxant. Int J Gynecol Obstet 2000, 70(Suppl. 1): Abst P2.15.24.
4. Kobayashi, M. et al. Pharmacological characterization of KUR-1246, a selective uterine relaxant. J Pharmacol Exp Ther 2001, 297(2): 666.
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DERMATOLOGIC DRUGS

ANTIPSORIATICS

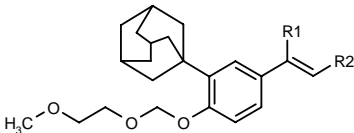
302913

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Compound	R1	R2	Isomer	Formula
302917	Me	4-CO2H-Ph	Z	C ₃₀ H ₃₆ O ₅
302920	Me	6-CO2H-3-Pyr	E	C ₂₉ H ₃₅ NO ₅
302922	Me	5-CO2H-2-Pyr	E	C ₂₉ H ₃₅ NO ₅
302961	H	4-CO2H-Ph	E	C ₂₈ H ₃₄ O ₅

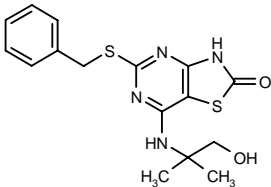
SOURCE – Galderma.

REFERENCES

1. Bernardon, J.-M. and Charpentier, B. (Laboratoires Galderma SA) *Stilbene cpds. comprising an adamantyl group; compsns. and methods thereof*. US 6214878.

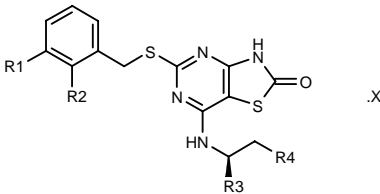
303674

5-(Benzylsulfanyl)-7-(2-hydroxy-1,1-dimethylethylamino)-thiazolo[4,5-d]pyrimidin-2(3H)-one



C16 H18 N4 O2 S2; Mol wt: 362.4762

ACTION – Chemokine CXCR2 receptor antagonist, potentially useful for the treatment of angiogenesis-related disorders and particularly claimed for the therapy of psoriasis. Other specifically claimed thiazolo[4,5-d]-pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
303676	H	H	Et	OH		C ₁₆ H ₁₈ N ₄ O ₂ S ₂
303678	F	F	H	OH		C ₁₄ H ₁₂ F ₂ N ₄ O ₂ S ₂
303680	Cl	F	Me	OH		C ₁₅ H ₁₄ ClFN ₄ O ₂ S ₂
303681	Cl	F	Me	NH2		C ₁₅ H ₁₅ ClFN ₅ OS ₂
303682	H	F	Me	OH		C ₁₅ H ₁₅ FN ₄ O ₂ S ₂
303683	H	Br	Me	OH		C ₁₅ H ₁₅ BrN ₄ O ₂ S ₂
303684	F	F	Me	ONa		C ₁₅ H ₁₃ F ₂ N ₄ NaO ₂ S ₂
303685	F	F	Me	NHCH2CH2OH	CF3CO2H	C ₁₇ H ₁₉ F ₂ N ₅ O ₂ S ₂ .C ₂ HF ₃ O ₂

SOURCE – AstraZeneca.

REFERENCES

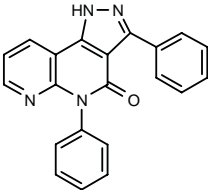
1. Willis, P.A. et al. (AstraZeneca plc) *Novel thiazolo(4,5-d)pyrimidine cpds*. WO 0125242.

HAIR GROWTH STIMULANTS

KF-19418*

193141

3,5-Diphenyl-4,5-dihydro-1H-pyrazolo[4,3-c][1,8]naphthyridin-4-one



C21 H14 N4 O; Mol wt: 338.3720

ACTION – Hair growth stimulant proven able to stimulate the proliferation of cultured hair bulb cells from newborn mice in a concentration-dependent manner at concentrations below 10 μM. It also induced hair follicle elongation in cultures of whole skin pieces from 4-week-old mice and this effect was superior to that of minoxidil. In a mouse model of alopecia, topical application of compound or minoxidil as a 1% suspension accelerated hair regrowth to a similar extent. Potentially useful for the treatment of human alopecia.

SOURCE – Kyowa Hakko.

REFERENCES

- 1. Suzuki, F. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Condensed naphthyridine derivs*. EP 0526840, JP 1993194515, US 5281610.
- 2. Shirai, A. et al. *KF19418, a new compound for hair growth promotion in vitro and in vivo mouse models*. J Dermatol Sci 2001, 25(3): 213.

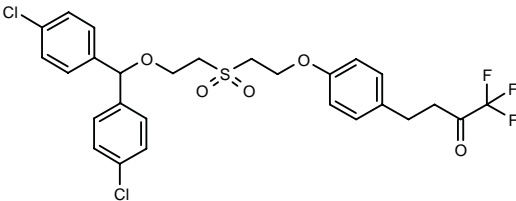
*Identified compound **193141** Drug Data Rep 1993, 015(06): 0502.

MISCELLANEOUS DERMATOLOGIC DRUGS

BMS-229724

306167

4-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylsulfonyl]-ethoxy]phenyl]-1,1,1-trifluorobutan-2-one



C27 H25 Cl2 F3 O5 S; Mol wt: 589.4555

ACTION – Antiinflammatory agent, a tight-binding inhibitor of cytosolic phospholipase A₂ (cPLA₂; IC₅₀ = 2.8 μM against human recombinant cPLA₂) with little or no activity against secretory PLA₂. In U-937 cells compound inhibited fMLP-stimulated arachidonate and PGE₂ production (IC₅₀ = 2 μM), but it was devoid of activity against phospholipase C or phospholipase D. Moreover, it inhibited arachidonate and eicosanoid production by a wide range of inflammatory cells including platelets, mast cells, keratinocytes and monocytes (IC₅₀ = 4-15 μM). In human monocytes, compound also inhibited the production of TNF-α, IL-6, IL-1β and IL-8 induced by lipopolysaccharide (LPS), with IC₅₀ values of 4-7 μM. Topical application of compound (5% w/v solution) significantly reduced edema and cell infiltration in a mouse model of chronic skin inflammation due to repeated exposure to phorbol ester, and it also markedly reduced prostaglandin and leukotriene biosynthesis in the inflamed skin. In hairless guinea pigs with UVB irradiation-induced skin erythema, compound dose-dependently (0.5-10 mg/kg p.o.) inhibited erythema, with a significant effect at 10 mg/kg p.o.; PGE₂ levels were significantly reduced at all doses.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Banville, J. et al. (Bristol-Myers Squibb Co.) *Selective cPLA₂ inhibitors*. WO 9915129.

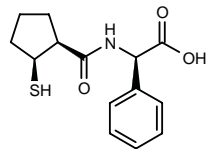
2. Burke, J.R. et al. *BMS-229724 is a tight-binding inhibitor of cytosolic phospholipase A2 that acts at the lipid/water interface and possesses anti-inflammatory activity in skin inflammation models*. J Pharmacol Exp Ther 2001, 298(1): 376.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

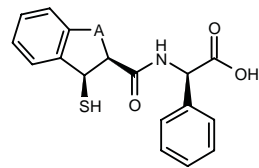
302366

cis-N-(2-Sulfanylcyclopentylcarbonyl)-D-phenylglycine



C14 H17 N O3 S; Mol wt: 279.3583

ACTION – Metallo-β-lactamase inhibitor active against enzymes produced by a wide range of microorganisms including both Gram-negative and Gram-positive bacteria. Other specifically claimed compounds from this series of pyrrolidine and thiazole derivatives are:



Compound	A	Formula
302367	-CH2-	C ₁₈ H ₁₇ NO ₃ S
302368	-(CH2)2-	C ₁₉ H ₁₉ NO ₃ S

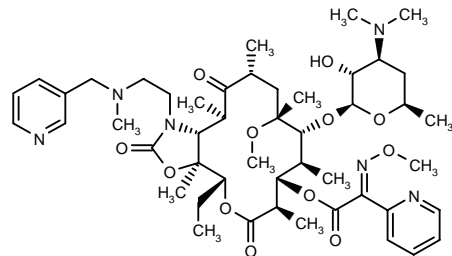
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bateson, J.H. and Best, D.J. (SmithKline Beecham plc) *Pyrrolidine and thiazole derivs. with metallo-β-lactamase inhibitory properties*. US 6211212, WO 9840056.

303548

11-Deoxy-3-*O*-des(hexopyranosyl)-3-*O*-[2-(methoxyimino)-2-(2-pyridyl)acetyl]-6-*O*-methyl-11-[2-[*N*-methyl-*N*-(pyridin-3-ylmethyl)amino]ethylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C48 H72 N6 O12; Mol wt: 925.1268

ACTION – Macrolide antibiotic, an erythromycin A derivative with more potent antibacterial activity than clarithromycin and azithromycin against *Staphylococcus aureus* B1 and *Streptococcus pneumoniae* 210 and 205 (MIC = 1.56, 0.39 and 0.20 μg/ml, respectively, vs. > 100, 0.78 and > 100 μg/ml, respectively, for clarithromycin, and > 100, 1.56 and > 100 μg/ml, respectively, for azithromycin).

SOURCE – Taisho.

REFERENCES

1. Asaga, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Macrolides*. JP 2001072699.

ACTION – Antiinflammatory agent, a tight-binding inhibitor of cytosolic phospholipase A₂ (cPLA₂; IC₅₀ = 2.8 μM against human recombinant cPLA₂) with little or no activity against secretory PLA₂. In U-937 cells compound inhibited fMLP-stimulated arachidonate and PGE₂ production (IC₅₀ = 2 μM), but it was devoid of activity against phospholipase C or phospholipase D. Moreover, it inhibited arachidonate and eicosanoid production by a wide range of inflammatory cells including platelets, mast cells, keratinocytes and monocytes (IC₅₀ = 4-15 μM). In human monocytes, compound also inhibited the production of TNF-α, IL-6, IL-1β and IL-8 induced by lipopolysaccharide (LPS), with IC₅₀ values of 4-7 μM. Topical application of compound (5% w/v solution) significantly reduced edema and cell infiltration in a mouse model of chronic skin inflammation due to repeated exposure to phorbol ester, and it also markedly reduced prostaglandin and leukotriene biosynthesis in the inflamed skin. In hairless guinea pigs with UVB irradiation-induced skin erythema, compound dose-dependently (0.5-10 mg/kg p.o.) inhibited erythema, with a significant effect at 10 mg/kg p.o.; PGE₂ levels were significantly reduced at all doses.

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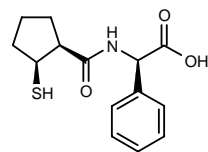
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ANTIINFECTIVE THERAPY

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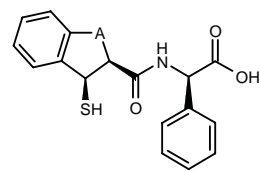
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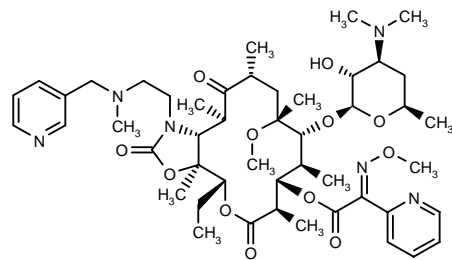
SOURCE – GlaxoSmithKline.

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SOURCE – Taisho.

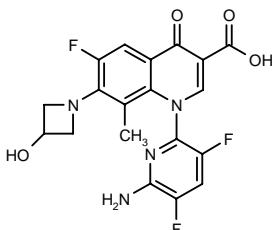
REFERENCES

1. Asaga, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Macrolides*. JP 2001072699.

ANTIBACTERIAL DRUGS

303028

1-(6-Amino-3,5-difluoropyridin-2-yl)-6-fluoro-7-(3-hydroxyazetidin-1-yl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C19 H15 F3 N4 O4; Mol wt: 420.3455

ACTION – Quinolone antibacterial agent with excellent antibacterial activity and high stability to light. *In vitro*, compound exhibited potent activity against *Staphylococcus aureus* 209P and Smith, methicillin-resistant *S. aureus* W200, *Staphylococcus epidermidis* IFO12293, *Bacillus subtilis* ATCC6633, *Escherichia coli* NIHJ-JC2, *Klebsiella pneumoniae* KC-1 and *Pseudomonas aeruginosa* IFO3445 (MIC = 0.006, < 0.003, 0.013, 0.013, 0.025, 0.05, 0.05 and 0.39 µg/ml, respectively), being superior to ciprofloxacin (MIC = 0.20, 0.20, 0.78, 0.78, 0.05, 0.013, 0.025 and 0.39 µg/ml, respectively) and levofloxacin (MIC = 0.20, 0.10, 0.39, 0.39, 0.10, 0.05, 0.05 and 0.78 µg/ml, respectively). In addition, it was devoid of phototoxicity in mice at 40 mg/kg i.v.

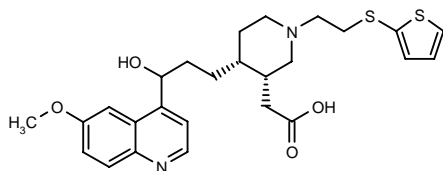
SOURCE – Wakunaga.

REFERENCES

1. Yazaki, A. et al. (Wakunaga Pharmaceutical Co., Ltd.) *Quinoline carboxylic acid deriv. or its salt*. WO 0117991.

303469

2-[4(*R*)-[3-Hydroxy-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-2-ylsulfanyl)ethyl]piperidin-3(*R*)-yl]acetic acid



C26 H32 N2 O4 S2; Mol wt: 500.6808

ACTION – Antibacterial agent reported to be active against Gram-positive and Gram-negative microorganisms such as methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecium* and *Moraxella catarrhalis*, and which exhibits low toxicity.

SOURCE – Aventis Pharma.

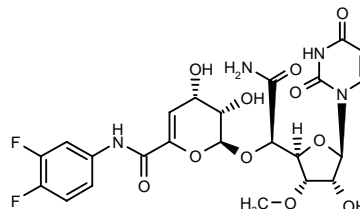
REFERENCES

1. Malleron, J.-L. et al. (Aventis Pharma SA) *Piperidine quinolyl propyl derivs., preparation method and compsns. containing same*. FR 2798656, WO 0125227.

ANTIMYCOBACTERIAL AGENTS

302116

5' (*R*)-Carbamoyl-5'-O-[(2*S*,3*S*,4*S*)-6-[*N*-(3,4-difluorophenyl)carbamoyl]-3,4-dihydroxy-3,4-dihydro-2*H*-pyran-2-yl]-3'-O-methyluridine



C23 H24 F2 N4 O11; Mol wt: 570.4556

ACTION – Antimycobacterial agent with MIC values of 2, 1 and 8 µg/ml, respectively, against *Mycobacterium avium* NIHJ1605, *Mycobacterium tuberculosis* Kato and *M. tuberculosis* No. 74. A representative compound from a series of A-500359 derivatives.

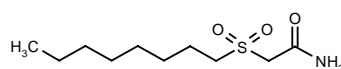
SOURCE – Sankyo.

REFERENCES

1. Hotoda, H. et al. (Sankyo Co., Ltd.) *Novel A-500359 derivs.* JP 2001192394, WO 0114399.

304960

2-(Octylsulfonyl)acetamide



C10 H21 N O3 S; Mol wt: 235.3459

ACTION – Antimycobacterial agent able to inhibit the growth of several species of slow-growing mycobacteria including wild-type and multidrug-resistant isolates of *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Mycobacterium bovis* and *Mycobacterium kansasii* (MIC = 6.25-12.5 µg/ml). Compound reduced mycolic acid accumulation in mycobacteria, probably by inhibition of fatty acid synthase. Potentially useful for the treatment of tuberculosis.

SOURCE – Johns Hopkins University, Baltimore, MD (US).

REFERENCES

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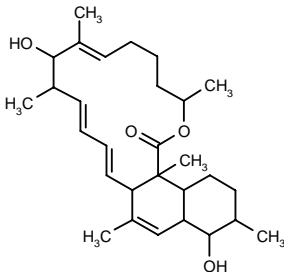
2. Jones, P.B. et al. *A new class of antituberculosis agents.* J Med Chem 2000, 43(17): 3304.

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TUBERACTOMYCIN B

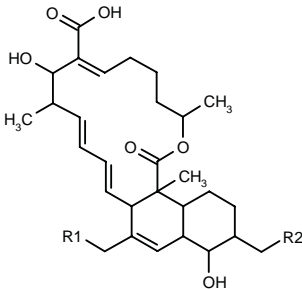
302985

9,17-Dihydroxy-3,8,10,15,18,20b-hexamethyl-3,4,5,6,9,10,14a,16a,17,18,19,20,20a,20b-tetradecahydro-1 *H*-naphtho[1,2-*c*]oxacyclohexadecin-1-one



C29 H44 O4; Mol wt: 456.6626

ACTION – Antibiotic isolated from *Nocardia* sp. MK703-102F1 (FERM P-16580), proven active *in vitro* against mycobacteria such as *Mycobacterium smegmatis* ATCC 607 (MIC = 0.39 µg/ml), a range of resistant *M. smegmatis* ATCC 607 strains (MIC = 0.20-0.39 µg/ml), *Mycobacterium phlei* (MIC = 0.39 µg/ml), *Mycobacterium vaccae* ATCC 15483 (MIC = 0.78 µg/ml) and *Mycobacterium fortuitum* (MIC = 6.25 µg/ml). Other compounds isolated from the same source are:



Compound	R1	R2	Formula
Tuberactomycin D [302986]	OH	H	C ₂₉ H ₄₂ O ₇
Tuberactomycin E [302987]	H	OH	C ₂₉ H ₄₂ O ₇

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

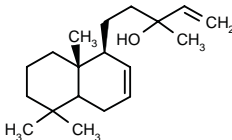
1. Takeuchi, T. et al. (Microbial Chemistry Research Foundation) *Antibiotics tuberactomycin B, D and E, and their preparation method*. JP 2001055386.

ANTIFUNGAL AGENTS

ALB-269

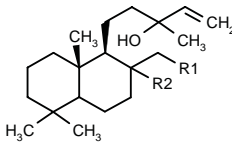
303585

cis-3-Methyl-5-(5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl)-1-penten-3-ol



C19 H32 O; Mol wt: 276.4608

ACTION – Antifungal agent, active against azole-sensitive and -resistant *Candida albicans* strains (IC₈₀ = 8 and 16 µg/ml, respectively). This compound was also active against *Aspergillus fumigatus* infection in mice, affording a survival rate of at least 60% at 10 mg/kg p.o. Other exemplified hydronaphthalene derivatives are:



Compound	R1	R2	Isomer	Formula
ALB-268 [303586]	allyl	OH		C ₂₃ H ₄₀ O ₂
ALB-270 [303587]	OH	OH	A	C ₂₀ H ₃₆ O ₃
ALB-271 [303588]	OH	OH	B	C ₂₀ H ₃₆ O ₃
ALB-272 [303589]	OH	H		C ₂₀ H ₃₆ O ₂
ALB-276 [303591]	cyclohexyl	OH		C ₂₆ H ₄₆ O ₂

SOURCE – Toagosei.

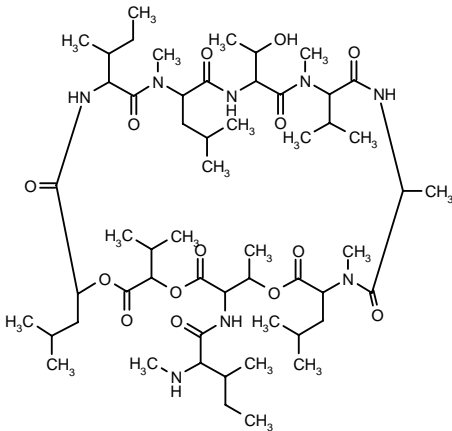
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F-15078A

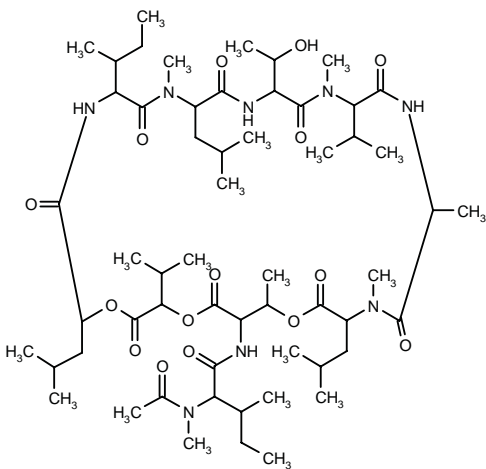
303036

N-[14-(1-Hydroxyethyl)-5,11,23-triisobutyl-2,17-diisopropyl-10,16,20,22,26-pentamethyl-8-(1-methylpropyl)-3,6,9,12,15,18,21,24,28-nonaoxo-1,4,25-trioxa-7,10,13,16,19,22-hexaazacyclooctacosan-27-yl]-3-methyl-2-(methylamino)pentanamide



C55 H98 N8 O14; Mol wt: 1095.4210

ACTION – Antifungal agent isolated from the fungus *Phoma* sp. SANK 13899 (FERM BP-6851), giving respective MIC values of 2.5, 1.3 and 0.31 µg/ml against *Candida albicans* ATCC 90028, *Aspergillus fumigatus* IAM 2034 and *Cryptococcus neoformans* IAM 4772. Another compound from the same source is:



F-15078B [303037]: C57 H100 N8 O15

SOURCE – Sankyo.

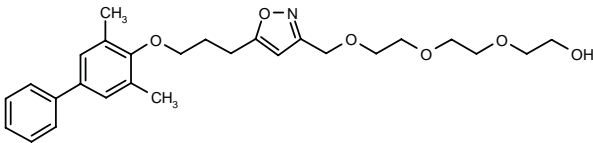
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ANTIVIRAL DRUGS

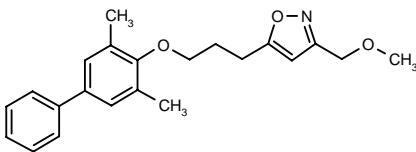
302628

2-[2-[2-[5-[3-(3,5-Dimethylbiphenyl-4-yloxy)propyl]isoxazol-3-ylmethoxy]ethoxy]ethoxy]ethanol

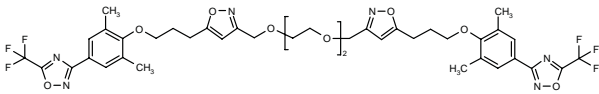


C27 H35 N O6; Mol wt: 469.5745

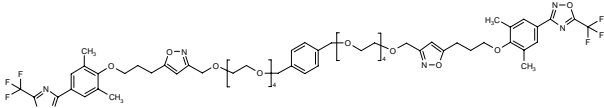
ACTION – Antiviral agent for the treatment of infections caused by picornaviruses, particularly human rhinovirus (HRV), as demonstrated against HRV-2 in infected human epidermoid carcinoma KB cells, where it exhibited an EC₅₀ value of 0.001 µg/ml, while displaying low cytotoxicity in uninfected cells (CC₅₀ = 5 µg/ml; selectivity index [SI] = 5,000). In addition, compound was found to be active against HRV-1A in infected human embryo lung MRC-5 cells (EC₅₀ = 0.59 µg/ml; CC₅₀ = 22.7 µg/ml; SI = 38.61). Within this series of compounds comprising two or more picornavirus capsid-binding moieties, the following are also exemplified:



302629: C22 H25 N O3



302631: C40 H42 F6 N6 O9



302632: C60 H74 F6 N6 O16

SOURCE – Biota Scientific Management.

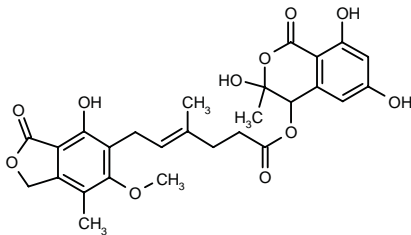
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1. Krippner, G. et al. (Biota Scientific Management Pty Ltd.) *Antiviral agents*. WO 0119822.

F-13459

305634

6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4(E)-hexenoic acid 3,6,8-trihydroxy-3-methyl-1-oxo-3,4-dihydro-1H-2-benzopyran-4-yl ester



C27 H28 O11; Mol wt: 528.5072

ACTION – Antiviral agent, a mycophenolic acid derivative isolated from the culture broth of *Penicillium* sp., with inhibitory activity on intracellular trafficking of viral glycoproteins. Both compound and mycophenolic acid inhibited viral glycoprotein hemagglutinin synthesis (80% inhibition at > 1.6 and 12.5 µg/ml, respectively) and syncytium formation (MIC = 0.4 and 3.2 µg/ml, respectively) in Newcastle disease virus-infected baby hamster kidney (BHK) cells.

SOURCES – Institute of Physical and Chemical Research (RIKEN), Saitama (JP); Nihon University, Tokyo (JP).

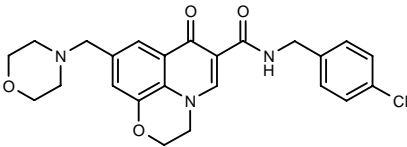
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PNU-246962^{1,2}

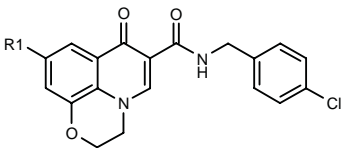
303471

N-(4-Chlorobenzyl)-9-(morpholin-4-ylmethyl)-7-oxo-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamide



C24 H24 Cl N3 O4; Mol wt: 453.9236

ACTION – Antiviral agent for the treatment of infections caused by viruses of the herpesvirus family such as cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, herpes simplex virus (HSV) and human herpesvirus type 8 (HHV-8) that acts by inhibiting viral DNA polymerase (IC₅₀ = 0.48 μM against HCMV polymerase). Other specifically claimed compounds from this series of oxazinoquinolones are:



Compound	R1	Formula
303473 ¹	ethynylene-CH2OH	C ₂₂ H ₁₇ ClN ₂ O ₄
303474 ¹	(CH2)3OH	C ₂₂ H ₂₁ ClN ₂ O ₄
303574 ¹	Pr	C ₂₂ H ₂₁ ClN ₂ O ₃

SOURCE – Pharmacia.

REFERENCES

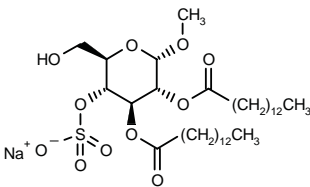
1. Turner, S.R. and Thaisrivongs, S. (Pharmacia Corp.) *Oxazinoquinolones useful for the treatment of viral infections*. WO 0125239.

2. Turner, S.R. et al. *Oxazinoquinolones as broad spectrum antiherpesvirus agents*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 175.

AIDS MEDICINES

302558

1-*O*-Methyl-4-*O*-sulfo-2,3-di-*O*-tetradecanoyl-α-D-glucopyranose sodium salt



C35 H65 Na O11 S; Mol wt: 716.9435

ACTION – Chemokine receptor antagonist, potentially useful for the treatment of a broad range of conditions including HIV infection, asthma, atopic dermatitis, rhinitis, conjunctivitis, nephritis, hepatitis, arthritis, transplant rejection and shock. *In vitro*, compound was shown to inhibit SDF-1-, MIP-3β/ELC-, MDC- and RANTES-induced transient increases in Ca²⁺ in CXCR4-, CCR7- and CCR4-expressing human T-cells and CCR5-expressing human monocytes, giving respective IC₅₀ values of 0.35, 0.17, 0.8 and 2.0 μM. In addition, it was found to inhibit the binding of HIV gp120 protein to anti-gp120 antibodies. A representative compound from a series of glucopyranose derivatives.

SOURCE – Ono.

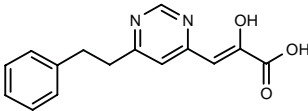
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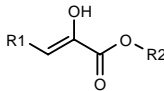
303060

2-Hydroxy-3-[6-(2-phenylethyl)pyrimidin-4-yl]-2(*Z*)-propenoic acid



C15 H14 N2 O3; Mol wt: 270.2866

ACTION – Anti-HIV agent, an integrase inhibitor with an IC₅₀ of 0.13 μg/ml against this enzyme. Other exemplified compounds are:



Compound	R1	R2	Formula
303065	5-(PhCH2O)-2-Pyr	Et	C ₁₇ H ₁₇ NO ₄
303066	5-(PhCH2O)-2-Pyr	H	C ₁₅ H ₁₃ NO ₄
303067	6-(PhCH2CH2)-4-pyrimidinyl	Et	C ₁₇ H ₁₈ N ₂ O ₃
303068	5-(PhCH2CH2)-1,3,4-thiadiazol-2-yl	H	C ₁₃ H ₁₂ N ₂ O ₃ S
303069	5-[2,4-(F)2-PhCH2O]-2-Pyr	Et	C ₁₇ H ₁₆ F ₂ NO ₄

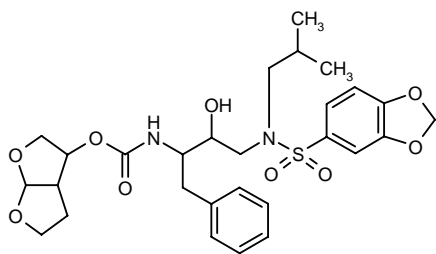
SOURCE – Shionogi.

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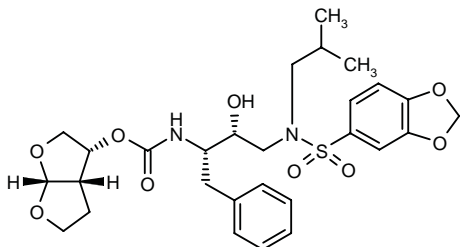
303422

N-[3-[*N*-(1,3-Benzodioxol-5-ylsulfonyl)-*N*-isobutylamino]-1-benzyl-2-hydroxypropyl]carbamic acid perhydrofuro-[2,3-*b*]furan-3-yl ester



C28 H36 N2 O9 S; Mol wt: 576.6634

ACTION – Antiviral agent for AIDS, a potent inhibitor of retroviral proteases, particularly multidrug-resistant retroviral proteases, with good oral bioavailability. *In vitro*, compound exhibited potent antiviral activity against HIV-1 strain LAI in MT-4 cells ($IC_{50} = 1.1$ nM; $IC_{90} = 2.4$ nM), with low cytotoxicity in uninfected cells ($CC_{50} = 15.3$ μ M; selectivity index = 13,900). When tested against a panel of resistant HIV strains, it exhibited IC_{50} values in the range 0.0003-0.0454 nM, showing greatly improved activity compared to saquinavir, ritonavir, indinavir, nelfinavir and amprenavir. Good oral bioavailability was demonstrated in rats following administration of 20 mg/kg p.o., serum concentrations reaching about 1 μ M at 1 h post-administration and exceeding the IC_{50} values against multidrug-resistant strains up to 3 h after dosing. A specifically claimed enantiomerically pure form is:



303423: C28 H36 N2 O9 S

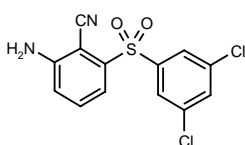
SOURCES – National Institutes of Health, Bethesda, MD (US); Tibotec.

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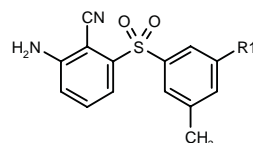
304494²

2-Amino-6-(3,5-dichlorophenylsulfonyl)benzonitrile



C13 H8 Cl2 N2 O2 S; Mol wt: 327.1902

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor ($IC_{50} = 30$ nM) with potent anti-HIV-1 activity ($IC_{50} = 70$ nM) and no cytotoxic activity in MT-4 cells ($CC_{50} > 200$ μ M). Compound retained potent activity against mutant viruses with resistance to nevirapine including V106A, P236L, E138K, V108L, G190A and Y188C mutants, being generally more potent than nevirapine but less than efavirenz; it was inactive against the key resistant strains K103N and Y181C and double mutants based on these two strains. Combination studies indicated synergistic interactions with other antiretrovirals including zidovudine, amprenavir, nevirapine and didanosine. In pharmacokinetic studies in rats, compound showed a mean half-life of 5.2 h and a mean clearance of 18 ml/min/kg following an i.v. dose of 2.5 mg/kg, with an oral bioavailability ranging from 4% to 18%. Other related compounds are:



Compound	R1	Formula
739W94 [228751]^{a,1-3}	Me	C ₁₅ H ₁₄ N ₂ O ₂ S
304495²	Cl	C ₁₄ H ₁₁ ClN ₂ O ₂ S

SOURCE – GlaxoSmithKline.

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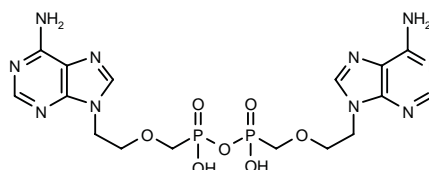
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- Hazen, R.J. et al. Antiviral and biological activities of 2-amino-6-arylsulfonylbenzonitrile analogues. Antivir Res 2001, 50(1): Abst 26.

^aIdentified compound **228751** Drug Data Rep 1996, 018(02): 0169.

BIS-PMEA

305614

*P*¹,*P*²-Bis[2-(adenin-9-yl)ethoxymethyl]diphosphonic acid



C16 H22 N10 O7 P2; Mol wt: 528.3608

ACTION – Antiviral prodrug of the nucleoside reverse transcriptase inhibitor PMEA (adefovir) encapsulated into autologous erythrocytes modified to increase their recognition and phagocytosis by human macrophages. Once inside the macrophages, the prodrug slowly degrades to give the active metabolite, which strongly protected against HIV-1 and HSV-1 infection (95 and 85% protection, respectively, at 0.9 μ M).

SOURCES – IRCCS “L. Spallanzani”, Roma (IT); Università degli Studi di Camerino, Camerino (IT); Università degli Studi Roma Tor Vergata, Roma (IT); Università degli Studi di Urbino, Urbino (IT).

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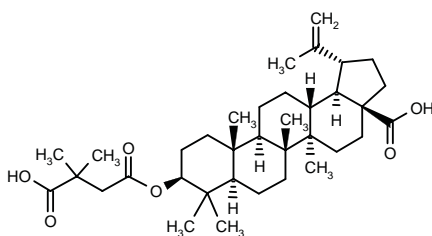
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YK-FH312*

246885

[1*S*-(1 α ,3 α ,5 α ,5 β ,7 α ,9 β ,11 α ,11 β ,13 α ,13 β)]-1-Isopropenyl-9-(3,3-dimethylsuccinyloxy)-5 α ,5 β ,8,8,11 α -pentamethylperhydrocyclopenta[*a*]chrysene-3 α -carboxylic acid

3 β -(3-Carboxy-3-methylbutanoyloxy)lup-20(29)-en-28-oic acid



C36 H56 O6; Mol wt: 584.8440

ACTION – Anti-HIV agent, a betulinic acid derivative proven to inhibit virus-induced cytopathic effect in HIV-1-infected MT-4 cells with an EC₅₀ of 0.011 μ g/ml. It was inactive in the syncytium formation inhibition assay, against HIV replication and did not inhibit HIV reverse transcriptase, indicating that it may act at the step of virion assembly and/or budding of virions.

SOURCES – Biotech Research Laboratories; University of North Carolina, Chapel Hill, NC (US).

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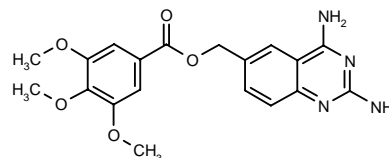
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*Identified compound **246885** (see **245900**) Drug Data Rep 1997, 019(05): 0445.

TREATMENT OF PROTOZOAL DISEASES

305379

3,4,5-Trimethoxybenzoic acid (2,4-diaminoquinazolin-6-yl)methyl ester



C19 H20 N4 O5; Mol wt: 384.3900

ACTION – Lipophilic soft drug dihydrofolate reductase inhibitor active against *Pneumocystis carinii* enzyme (IC₅₀ = 0.56 μ M), with very low systemic bioavailability and suitable for inhalation therapy of *P. carinii* infection.

SOURCES – Indiana University, Indianapolis, IN (US); Uppsala University, Uppsala (SE).

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DU-1102

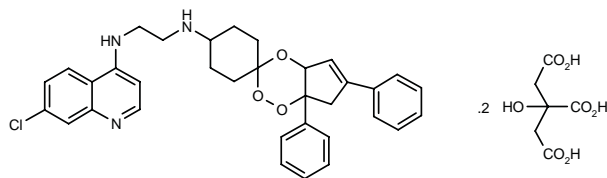
304931

*N*¹-(7-Chloroquinolin-4-yl)-*N*²-[6',7'-a-diphenyl-7',7'-a-dihydrospiro[cyclohexane-1,3'-4'*a*H-cyclopenta-[1,2,4]trioxin]-4-yl]ethane-1,2-diamine dicitrate

ODC-218

DU-1101 (as free base)

ODC-188 (as free base)



C34 H34 Cl N3 O3 . 2 C6 H8 O7; Mol wt: 952.3580

ACTION – Antimalarial agent, a chimeric molecule that combines the ability of the 4-aminoquinoline moiety to penetrate infected erythrocytes with the alkylating properties of the trioxane residue. Compound exhibited strong antimalarial activity against a broad range of *Plasmodium falciparum* isolates including chloroquine- and pyrimethamine-resistant isolates (MIC₅₀ = 43 nmol/l). DU-1102 has also demonstrated oral activity in mice infected with *Plasmodium berghei*.

SOURCES – CNRS; Palumed.

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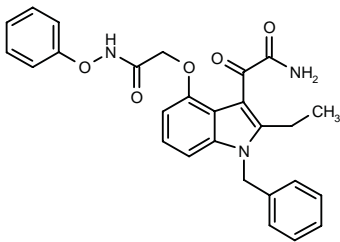
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TREATMENT OF SEPTIC SHOCK

303172

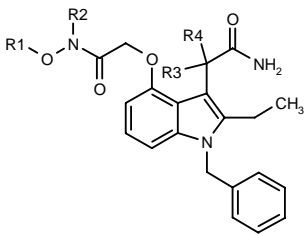
2-[1-Benzyl-2-ethyl-4-[2-oxo-2-(phenoxyamino)ethoxy]-1*H*-indol-3-yl]-2-oxoacetamide

2-[3-(2-Amino-2-oxoacetyl)-1-benzyl-2-ethyl-1*H*-indol-4-yloxy]acetohydroxamic acid phenyl ester



C27 H25 N3 O5; Mol wt: 471.5105

ACTION – A human nonpancreatic secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 9.0 ± 2.0 nM for inhibition of recombinant human sPLA₂) that is expected to be useful for the treatment of inflammatory disorders such as septic shock. Other exemplified indole compounds include the following:



Compound	R1	R2	R3	R4	Formula
303173	H	H	-O-		C ₂₁ H ₂₁ N ₃ O ₅
303174	Me	H	-O-		C ₂₂ H ₂₃ N ₃ O ₅
303175	Me	Me	-O-		C ₂₃ H ₂₅ N ₃ O ₅
303176	H	Me	-O-		C ₂₂ H ₂₃ N ₃ O ₅
303177	Et	H	-O-		C ₂₃ H ₂₅ N ₃ O ₅
303178	allyl	H	-O-		C ₂₄ H ₂₅ N ₃ O ₅
303179	H	i-Pr	-O-		C ₂₄ H ₂₇ N ₃ O ₅
303180	t-Bu	H	-O-		C ₂₅ H ₂₉ N ₃ O ₅
303181	i-Bu	H	-O-		C ₂₅ H ₂₉ N ₃ O ₅
303182	CH2Ph	H	-O-		C ₂₈ H ₂₇ N ₃ O ₅
303183	CH2Ph	Me	-O-		C ₂₉ H ₂₉ N ₃ O ₅
303184	Ph	Me	-O-		C ₂₈ H ₂₇ N ₃ O ₅
303185	H	cyclohexyl	-O-		C ₂₇ H ₃₁ N ₃ O ₅
303186	H	H	H	H	C ₂₁ H ₂₃ N ₃ O ₄
303187	H	CH2Ph	-O-		C ₂₈ H ₂₇ N ₃ O ₅

SOURCE – Lilly.

REFERENCES

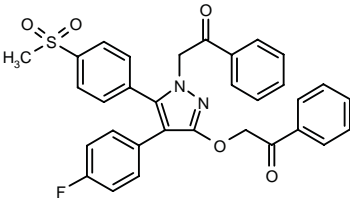
1. Harper, R.W. et al. (Eli Lilly and Company) Novel sPLA₂ inhibitors. WO 0121587.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

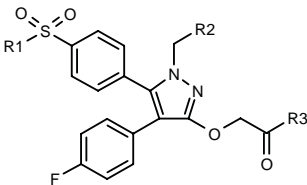
302343

2-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(2-oxo-2-phenylethoxy)-1*H*-pyrazol-1-yl]-1-phenylethanone

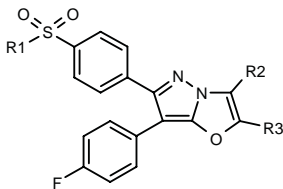


C32 H25 F N2 O5 S; Mol wt: 568.6225

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor proven active *in vivo* in the carrageenan-induced pleural inflammation model in rats (38% inhibition at 10 mg/kg p.o.). Other exemplified compounds from this series of sulfonylphenylpyrazole derivatives include the following:



Compound	R1	R2	R3	Formula
302345	Me	4-F-PhCO	4-F-Ph	C ₃₂ H ₂₃ F ₃ N ₂ O ₅ S
302346	Me	Me	t-Bu	C ₂₄ H ₂₇ N ₂ O ₄ S
302348	Me	Me	2-thienyl	C ₂₄ H ₂₁ FN ₂ O ₄ S ₂
302349	NH2	Me	t-Bu	C ₂₃ H ₂₆ FN ₃ O ₄ S



Compound	R1	R2	R3	Formula
302350	Me	-(CH2)4-		C ₂₂ H ₁₉ FN ₂ O ₃ S
302351	NH2	t-Bu	H	C ₂₁ H ₂₀ FN ₃ O ₃ S
302352	NH2	Me	CN	C ₁₉ H ₁₃ FN ₄ O ₃ S
302353	Me	Et	H	C ₂₀ H ₁₇ FN ₂ O ₃ S
302354	NH2	Et	H	C ₁₉ H ₁₆ FN ₃ O ₃ S

2. Basco, L.K. et al. *In vitro* activities of DU-1102, a new trioxaquine derivative, against *Plasmodium falciparum* isolates. Antimicrob Agents Chemother 2001, 45(6): 1886.

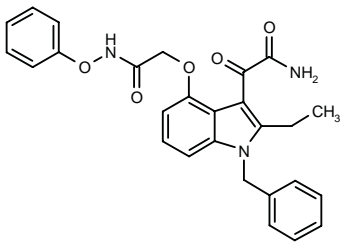
3. Dechy-Cabaret, O. et al. Preparation and antimalarial activities of "trioxaquines", new modular molecules with a trioxane squeleton linked to a 4-aminoquinoline. Chem Bio Chem 2000, 1(4): 281.

TREATMENT OF SEPTIC SHOCK

303172

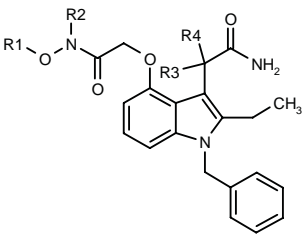
2-[1-Benzyl-2-ethyl-4-[2-oxo-2-(phenoxyamino)ethoxy]-1*H*-indol-3-yl]-2-oxoacetamide

2-[3-(2-Amino-2-oxoacetyl)-1-benzyl-2-ethyl-1*H*-indol-4-yloxy]acetohydroxamic acid phenyl ester



C27 H25 N3 O5; Mol wt: 471.5105

ACTION – A human nonpancreatic secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 9.0 ± 2.0 nM for inhibition of recombinant human sPLA₂) that is expected to be useful for the treatment of inflammatory disorders such as septic shock. Other exemplified indole compounds include the following:



Compound	R1	R2	R3	R4	Formula
303173	H	H	-O-		C ₂₁ H ₂₁ N ₃ O ₅
303174	Me	H	-O-		C ₂₂ H ₂₃ N ₃ O ₅
303175	Me	Me	-O-		C ₂₃ H ₂₅ N ₃ O ₅
303176	H	Me	-O-		C ₂₂ H ₂₃ N ₃ O ₅
303177	Et	H	-O-		C ₂₃ H ₂₅ N ₃ O ₅
303178	allyl	H	-O-		C ₂₄ H ₂₅ N ₃ O ₅
303179	H	i-Pr	-O-		C ₂₄ H ₂₇ N ₃ O ₅
303180	t-Bu	H	-O-		C ₂₅ H ₂₉ N ₃ O ₅
303181	i-Bu	H	-O-		C ₂₅ H ₂₉ N ₃ O ₅
303182	CH2Ph	H	-O-		C ₂₈ H ₂₇ N ₃ O ₅
303183	CH2Ph	Me	-O-		C ₂₉ H ₂₉ N ₃ O ₅
303184	Ph	Me	-O-		C ₂₈ H ₂₇ N ₃ O ₅
303185	H	cyclohexyl	-O-		C ₂₇ H ₃₁ N ₃ O ₅
303186	H	H	H	H	C ₂₁ H ₂₃ N ₃ O ₄
303187	H	CH2Ph	-O-		C ₂₈ H ₂₇ N ₃ O ₅

SOURCE – Lilly.

REFERENCES

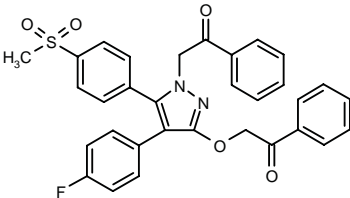
1. Harper, R.W. et al. (Eli Lilly and Company) Novel sPLA₂ inhibitors. WO 0121587.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

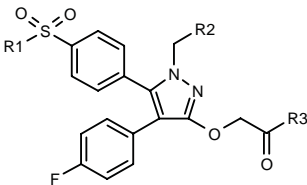
302343

2-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(2-oxo-2-phenylethoxy)-1*H*-pyrazol-1-yl]-1-phenylethanone

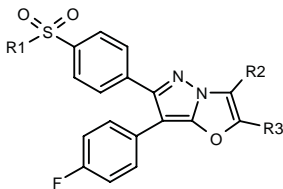


C32 H25 F N2 O5 S; Mol wt: 568.6225

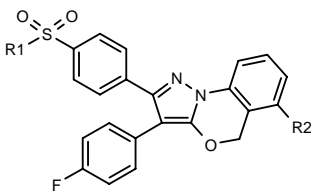
ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor proven active *in vivo* in the carrageenan-induced pleural inflammation model in rats (38% inhibition at 10 mg/kg p.o.). Other exemplified compounds from this series of sulfonylphenylpyrazole derivatives include the following:



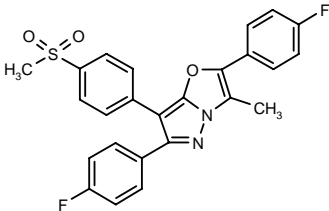
Compound	R1	R2	R3	Formula
302345	Me	4-F-PhCO	4-F-Ph	C ₃₂ H ₂₃ F ₃ N ₂ O ₅ S
302346	Me	Me	t-Bu	C ₂₄ H ₂₇ N ₂ O ₄ S
302348	Me	Me	2-thienyl	C ₂₄ H ₂₁ FN ₂ O ₄ S ₂
302349	NH2	Me	t-Bu	C ₂₃ H ₂₆ FN ₃ O ₄ S



Compound	R1	R2	R3	Formula
302350	Me	-(CH2)4-		C ₂₂ H ₁₉ FN ₂ O ₃ S
302351	NH2	t-Bu	H	C ₂₁ H ₂₀ FN ₃ O ₃ S
302352	NH2	Me	CN	C ₁₉ H ₁₃ FN ₄ O ₃ S
302353	Me	Et	H	C ₂₀ H ₁₇ FN ₂ O ₃ S
302354	NH2	Et	H	C ₁₉ H ₁₆ FN ₃ O ₃ S



Compound	R1	R2	Formula
302347	Me	H	C ₂₃ H ₁₇ FN ₂ O ₃ S
302355	Me	Cl	C ₂₃ H ₁₆ ClFN ₂ O ₃ S
302356	NH2	H	C ₂₂ H ₁₆ FN ₃ O ₃ S



302357: C25 H18 F2 N2 O3 S

SOURCE – Abbott.

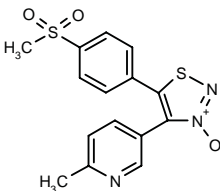
REFERENCES

1. Kolasa, T. and Patel, M.V. (Abbott Laboratories Inc.) *Sulfonylphenylpyrazole cpds. useful as COX-2 inhibitors*. WO 0116138.

302414

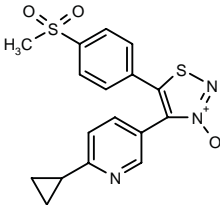
2-Methyl-5-[5-[4-(methylsulfonyl)phenyl]-3-oxido-1,2,3-thiadiazol-4-yl]pyridine

4-(6-Methylpyridin-3-yl)-5-[4-(methylsulfonyl)phenyl]-1,2,3-thiadiazol-3-oxide



C15 H13 N3 O3 S2; Mol wt: 347.4177

ACTION – Antiinflammatory agent, a selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 1.1 μM vs. 12.6 μM for COX-1). Another exemplified compound from this series of 1,2,3-thiadiazoles is:



302415: C17 H15 N3 O3 S2

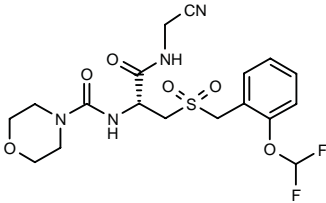
SOURCE – Merck Frosst.

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1. Lau, C.K. et al. (Merck Frosst Canada Inc.) *1,2,3-Thiadiazoles and their use as COX-2 inhibitors*. WO 0117996.

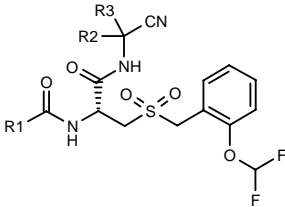
302689

N-[2-(Cyanomethylamino)-1(R)-[2-(difluoromethoxy)benzylsulfonylmethyl]-2-oxoethyl]morpholine-4-carboxamide



C18 H22 F2 N4 O6 S; Mol wt: 460.4558

ACTION – Potent and selective inhibitor of cathepsin S reported to exhibit at least 50-fold selectivity over cathepsin K, with potential for the treatment of autoimmune diseases such as juvenile-onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves’ disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto’s thyroiditis, as well as allergic disorders such as asthma, transplant rejection, disorders involving excessive elastolysis such as chronic obstructive pulmonary disease, cardiovascular disorders such as plaque rupture and atheroma, and systemic amyloidosis. Other specifically claimed compounds from this series of nitrile derivatives are:



Compound	R1	R2	R3	Formula
302690	2-thienyl	H	H	C ₁₈ H ₁₇ F ₂ N ₃ O ₅ S ₂
302691	3-thienyl	H	H	C ₁₈ H ₁₇ F ₂ N ₃ O ₅ S ₂
302692	4-F-Ph	H	H	C ₂₀ H ₁₈ F ₃ N ₃ O ₅ S
302693	4-morpholinyl	-CH2CH2N(Me)CH2CH2-		C ₂₃ H ₃₁ F ₂ N ₅ O ₆ S
302694	5-Me-2-thienyl	H	H	C ₁₉ H ₁₉ F ₂ N ₃ O ₅ S ₂
302695	5-indolyl	H	H	C ₂₂ H ₂₀ F ₂ N ₃ O ₅ S
302696	3-Me-Ph	H	H	C ₂₁ H ₂₁ F ₂ N ₃ O ₅ S
302697	3,4-(F)2-Ph	H	H	C ₂₀ H ₁₇ F ₄ N ₃ O ₅ S
302699	4-Pyr	H	H	C ₁₉ H ₁₈ F ₂ N ₄ O ₅ S
302700	4-morpholinyl	-CH2CH2-		C ₂₀ H ₂₄ F ₂ N ₄ O ₆ S

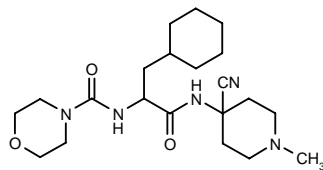
SOURCE – Axys Pharmaceuticals.

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1. Graupe, M. et al. (Axys Pharmaceuticals, Inc.) *Chemical cpds. and pharmaceutical compsns. as cathepsin S inhibitors*. WO 0119796, WO 0119808.

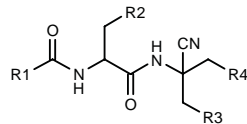
302760

N-[1-[N-(4-Cyano-1-methylpiperidin-4-yl)carbamoyl]-2-cyclohexylethyl]morpholine-4-carboxamide



C21 H35 N5 O3; Mol wt: 405.5395

ACTION – Reversible inhibitor of cathepsin S, K, F, L and/or B, with potential for the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Graves’ disease, myasthenia gravis, scleroderma, glomerulonephritis, atopic dermatitis and insulin-dependent diabetes mellitus, as well as Alzheimer’s disease, atherosclerosis, osteoporosis and asthma. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
302761	4-morpholinyl	cyclohexyl	-CH2NHCH2-		C ₂₀ H ₃₄ ClN ₅ O ₃
302762	5-Cl-2-thienyl	cyclohexyl	-CH2N(Me)CH2-		C ₂₁ H ₂₉ ClN ₄ O ₂ S
302763	2-pyrazinyl	t-Bu	-N(CH2Ph)CH2-		C ₂₄ H ₃₀ N ₆ O ₂
302764	4-morpholinyl	cyclohexyl	-N(Et)CH2-		C ₂₁ H ₃₅ N ₅ O ₃
302765	4-morpholinyl	cyclohexyl	-N(CH2Ph)-		C ₂₆ H ₃₅ N ₅ O ₃
302766	4-morpholinyl	cyclohexyl	-CH2NH-		C ₁₉ H ₃₁ N ₅ O ₃
302767	4-Cl-Ph	t-Bu	-CH2N(Pr)CH2-		C ₂₃ H ₃₃ ClN ₄ O ₂
302768	4-morpholinyl	t-Bu	-CH(Me)N(Me)CH2-		C ₂₀ H ₃₅ N ₅ O ₃

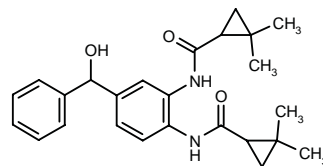
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Emmanuel, M.J. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Novel spiroheterocyclic cpds. useful as reversible inhibitors of cysteine proteases.* WO 0119816.

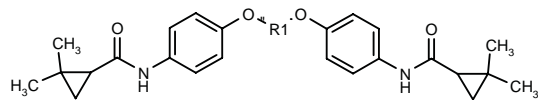
302944

N,N’-[4-(1-Hydroxy-1-phenylmethyl)-1,2-phenylene]-bis(2,2-dimethylcyclopropanecarboxamide)



C25 H30 N2 O3; Mol wt: 406.5230

ACTION – An inhibitor of NF-κB activation also reported to inhibit inflammatory cytokine production, matrix metallo-proteinases and cell adhesion factor expression, with potential as an antiinflammatory, antirheumatic, immuno-suppressant, antimetastatic and antiviral agent. *In vitro*, compound inhibited IL-1β-stimulated NF-κB activity in human umbilical vein endothelial cells (HUVEC) with an IC₅₀ of 1 μg/ml. Other compounds from this series of biscyclopropanecarboxylic acid amide derivatives include the following:



Compound	R1	Formula
302945	-1,3-Ph-	C ₃₀ H ₃₂ N ₂ O ₄
302946	-1,4-Ph-	C ₃₀ H ₃₂ N ₂ O ₄

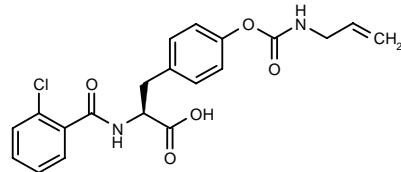
SOURCE – Ajinomoto.

REFERENCES

1. Iino, Y. et al. (Ajinomoto Co., Inc.) *Biscyclopropanecarboxylic acid amide cpds. and medicinal use thereof.* WO 0116091.

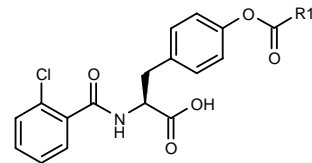
303105

4-O-(N-Allylcarbamoyl)-N-(2-chlorobenzoyl)-L-tyrosine



C20 H19 Cl N2 O5; Mol wt: 402.8321

ACTION – An inhibitor of the binding of α₄β₇ or α₄β₁ integrins to their ligands mucosal addressin cell adhesion molecule (MAdCAM) and/or vascular endothelial cell adhesion molecule (VCAM), potentially useful for the treatment of a broad range of disorders including arthritis, asthma, psoriasis, multiple sclerosis, Crohn’s disease, ulcerative colitis, pancreatitis, graft-versus-host disease, insulin-dependent diabetes mellitus, chronic bronchitis and systemic lupus erythematosus. Other exemplified compounds from this series of tyrosine derivatives and related compounds include the following:



Compound	R1	Formula
303106	NHPr	C ₂₀ H ₂₁ ClN ₂ O ₅
303107	NHCH2CH2Ph	C ₂₅ H ₂₃ ClN ₂ O ₅
303109	(R)-3-MeO-PhCH(Me)NH	C ₂₆ H ₂₅ ClN ₂ O ₆
303111	1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₆ H ₂₃ ClN ₂ O ₅
303112	3-MeO-PhCH2CH2NH	C ₂₆ H ₂₅ ClN ₂ O ₆
303114	6,7-(MeO)2-1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₈ H ₂₇ ClN ₂ O ₇
303116	N(Me)CH2CH2CN	C ₂₁ H ₂₀ ClN ₃ O ₅

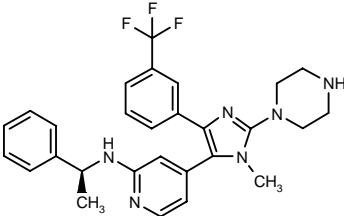
SOURCE – Genentech.

REFERENCES

1. Jackson, D.Y. et al. (Genentech, Inc.) *Tyrosine derivs.* WO 0121584.

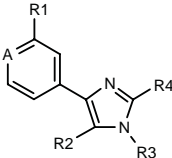
303385

4-[1-Methyl-2-(1-piperazinyl)-4-[3-(trifluoromethyl)phenyl]-1*H*-imidazol-5-yl]-*N*-[1(*S*)-phenylethyl]pyridin-2-amine

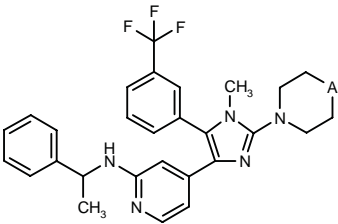


C28 H29 F3 N6; Mol wt: 506.5731

ACTION – An inhibitor of the activity of cytokines such as IL-1, IL-6, IL-8 and TNF that is expected to be useful for the treatment of rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, osteoporosis and Crohn’s disease, among others. Other specifically claimed substituted imidazoles include the following:



Compound	R1	R2	R3	R4	A	Formula
303386	CF3	(S)-2-[PhCH(Me)NH]-4-Pyr	Me	NHMe	CH	C ₂₅ H ₂₄ F ₃ N ₅
303389	CF3	(R)-2-[PhCH(Me)NH]-4-Pyr	H	1-Pip	CH	C ₂₈ H ₂₈ F ₃ N ₅
303390	H	4-F-Ph	H	1-Pip	N	C ₁₉ H ₁₉ FN ₄
303393	CF3	(S)-2-[PhCH(Me)NH]-4-Pyr	H	1-Pip	CH	C ₂₈ H ₂₈ F ₃ N ₅



Compound	A	Isomer	Formula
303387	CH2	R	C ₂₉ H ₃₀ F ₃ N ₅
303388	NH	R	C ₂₈ H ₂₉ F ₃ N ₆
303391	CH2	S	C ₂₉ H ₃₀ F ₃ N ₅
303392	NH	S	C ₂₈ H ₂₉ F ₃ N ₆

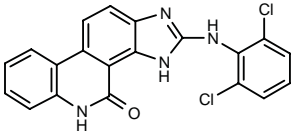
SOURCE – Merck & Co.

REFERENCES

1. Claiborne, C.F. et al. (Merck & Co., Inc.) *Substd. imidazoles having cytokine inhibitory activity.* WO 0122965.

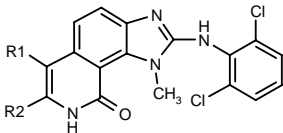
303501¹

2-(2,6-Dichlorophenylamino)-4,5-dihydro-3*H*-imidazo-[4,5-*l*]phenanthridin-4-one



C20 H12 Cl2 N4 O; Mol wt: 395.2478

ACTION – Tyrosine kinase inhibitor that particularly inhibits platelet-derived growth factor receptor (PDGFR) kinase and Src family kinases. Potentially useful for the treatment of autoimmune diseases, transplant rejection, psoriasis, osteoporosis, Paget’s disease, cancer, atherosclerosis, restenosis and allergic diseases Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	Formula
303503 ^{1,2}	H	CH=CHCO2Me	C ₂₁ H ₁₆ Cl ₂ N ₄ O ₃
303504 ¹	H	CH=CHCONHCH2Ph	C ₂₇ H ₂₁ Cl ₂ N ₅ O ₂
303505 ^{1,2}	Me	5-oxazolyl	C ₂₁ H ₁₅ Cl ₂ N ₅ O ₂
303506 ^{1,2}	H	5-oxazolyl	C ₂₀ H ₁₃ Cl ₂ N ₅ O ₂
303509 ¹	Me	CH=CHCH2N(Me)CH2CH2N(Et)2	C ₂₈ H ₃₄ Cl ₂ N ₆ O

SOURCE – Boehringer Ingelheim.

REFERENCES

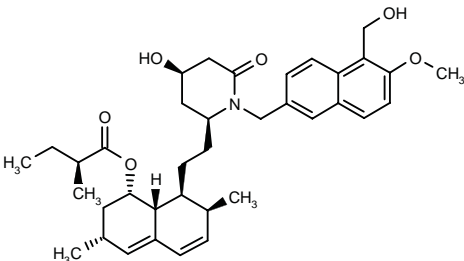
1. Snow, R.J. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Heterocyclic cpds. useful as inhibitors of tyrosine kinases.* WO 0125238.

2. Hammach, A. et al. *2-Phenylamino-imidazo[4,5-h]isoquinolin-9-ones novel and highly active inhibitors of LCK kinase.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 265.

LFA-703*

293871

2(*S*)-Methylbutyric acid (1*S*,3*R*,7*S*,8*S*,8*aR*)-8-[2-[4(*R*)-hydroxy-1-[5-(hydroxymethyl)-6-methoxynaphthalen-2(*S*)-ylmethyl]-6-oxopiperidin-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8*a*-hexahydronaphthalen-1-yl ester



C37 H49 N O6; Mol wt: 603.7951

ACTION – Statin compound with potent and selective inhibitory activity against LFA-1 (lymphocyte function-associated antigen-1)- mediated leukocyte adhesion to ICAM-1 (IC_{50} = 0.2 and 0.7 μ M in binding and HUT78 adhesion assay, respectively) by binding to a novel allosteric site within LFA-1. *In vivo*, compound inhibited peritonitis induced in mice by thioglycollate with an ED_{50} of 0.4 μ g/kg p.o. Potentially useful for the treatment of rheumatoid arthritis, psoriasis, ischemia/reperfusion injury and transplant rejection.

SOURCE – Novartis.

REFERENCES

1. Banteli, R. et al. (Novartis AG) *Mevinolin derivs.* WO 0048989.
2. Weitz-Schmidt, G. et al. *Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site.* Nat Med 2001, 7(6): 687.

*Identified compound **293871** (see **293870**) Drug Data Rep 2001, 023(01): 0075.

MRA

276293

Humanized anti-human interleukin-6 receptor (anti-hIL-6R) monoclonal antibody derived from the murine PM-1 antibody

Anti-IL-6 receptor MAb

ACTION – Humanized anti- IL-6 receptor antibody able to block the *in vivo* functions of IL-6. In monkeys, a single pretreatment with this MAb completely inhibited the changes induced by repeated administration of IL-6 for 7 days, such as the increase in blood platelet count and serum C-reactive protein (CRP) levels. In a model of collagen-induced arthritis in monkeys, the MAb given at a dose of 10 mg/kg i.v. once a week for 13 weeks suppressed the onset of clinical signs of arthritis such as stiff joints and swelling, and reduced histological changes and inflammatory parameters such as CRP, fibrinogen and erythrocyte sedimentation rate. The MAb was well tolerated and did not induce changes in body weight or hematological parameters. In a preliminary study in rheumatoid arthritis (RA) patients, 2 months' treatment with the MAb significantly improved RA symptoms and reduced the serum levels of the matrix metalloproteinase stromelysin 1 (MMP-3). Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Chugai.

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1. Katsume, T. and Saito, H. (Chugai Pharmaceutical Co. Ltd.) *Remedy for diseases caused by IL-6 production.* EP 0791359, JP 1996169846, WO 9612503.
2. Mihara, M. et al. (Chugai Pharmaceutical Co. Ltd.) *Rheumatoid arthritis remedy containing IL-6 antagonist as active ingredient.* EP 0783893, WO 9611020.
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5. Mihara, M. et al. *Humanized antibody to human interleukin-6 receptor inhibits the development of collagen arthritis in cynomolgus monkeys.* Clin Immunol 2001, 98(3): 319.
6. Nishimoto, N. et al. *Anti-interleukin 6 receptor antibody treatment in rheumatic disease.* Ann Rheum Dis 2000, 59(Suppl. 1): I21.

7. Nishimoto, N. et al. *Reduction of serum matrix metalloproteinase-3 in rheumatoid arthritis patients following anti-IL-6 receptor antibody therapy.* 64th Annu Meet Am Coll Rheumatol (Oct 29-Nov 2, Philadelphia) 2000, Abstr 100.

8. Shinkura, H. et al. *In vivo blocking effects of a humanized antibody to human interleukin-6 receptor on interleukin-6 function in primates.* Anticancer Res 1998, 18(2A): 1217.

9. Yoshizaki, K. and Nishimoto, N. *A new therapy for rheumatoid arthritis with a humanized anti IL-6 receptor antibody, MRA.* Ryumachi 2001, 41(2): 303.

10. *Chugai reports progress in the development of new antiarthritis.* DailyDrugNews.com (Daily Essentials) 1999, Nov 15.

11. *Chugai reviews progress of selected product candidates at end of fiscal year.* DailyDrugNews.com (Daily Essentials) 1999, May 31.

12. *Chugai to begin clinical testing of anti-IL-6 receptor antibody.* DailyDrugNews.com (Daily Essentials) 1998, July 6.

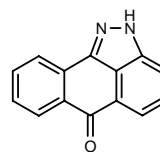
13. *Development Pipeline.* Chugai Pharmaceutical Web Site 2001, May 21.

14. *Three products advance in the pipeline at Chugai.* DailyDrugNews.com (Daily Essentials) 1999, March 22.

SP-600125*

301539

Anthra[1,9-*cd*]pyrazol-6(2*H*)-one



C₁₄ H₈ N₂ O; Mol wt: 220.2302

ACTION – Potent and selective inhibitor of c-Jun N-terminal kinase (JNK) with IC_{50} values of 0.11-0.15 μ M against JNK1, JNK2 and JNK3 versus values of > 10 μ M against most other enzymes tested. Compound was able to completely suppress IL-1-induced c-Jun activity, accumulation of phospho-Jun and induction of c-Jun transcription in human fibroblast-like synoviocytes at a concentration of 20 μ M, as well as AP-1 binding and collagenase mRNA expression. In contrast, the MEK inhibitor PD-98059 and the p38 α / β inhibitor SB-203580 had little or no effect in these assays. In rats with adjuvant-induced arthritis, treatment with SP-600125 at a dose of 30 mg/kg/day s.c. was associated with inhibition of JNK function in joints, a reduction in paw swelling and almost complete protection against bone and cartilage damage, as well as significant decreases in joint collagenase mRNA and AP-1 binding. In a model of asthma characterized by airways hyperresponsiveness to allergen and inflammation in sensitized rats repeatedly exposed to allergen, compound given i.p. at a dose of 30 mg/kg/day significantly reduced the increase in inflammatory cells (eosinophils, lymphocytes) in broncho-alveolar lavage fluid and significantly reduced serum levels of IgE, but had no effect on allergen-induced airways hyperresponsiveness. Potentially useful for the treatment of rheumatoid arthritis and asthma.

SOURCE – Celgene.

REFERENCES

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2. Bennett, B. et al. *SP600125, a selective inhibitor of JNK that modulates the activation and differentiation of CD4+ cells.* Inflamm Res 2000, 49(Suppl. 2): S102.

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4. Eynott, P.R. et al. *The effects of selective c-jun NH2-terminal kinase inhibition in a sensitized Brown-Norway rat model of allergic asthma*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A434.

5. Han, Z. et al. *C-jun N-terminal kinase is required for metalloproteinase (MMP) expression in synoviocytes and regulates bone destruction in adjuvant arthritis*. 64th Annu Meet Am Coll Rheumatol (Oct 29-Nov 2, Philadelphia) 2000, Abst 1988.

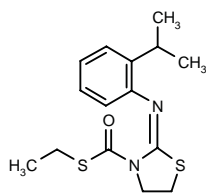
6. Han, Z. et al. *c-Jun N-terminal kinase is required for metalloproteinase expression and joint destruction in inflammatory arthritis*. J Clin Invest 2001, 108(1): 73.

*Identified compound **301539** Drug Data Rep 2001, 023(07): 0694.

IMMUNOMODULATING AGENTS

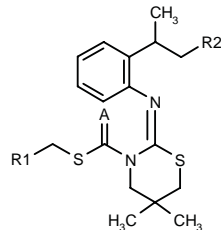
303120

2-(2-Isopropylphenylimino)thiazolidine-3-carbothioic acid S-ethyl ester



C15 H20 N2 O S2; Mol wt: 308.4680

ACTION – High-affinity cannabinoid CB₂ receptor ligand, as demonstrated by K_i values of 9 and > 5000 nM against [³H]-CP-55940 binding to human CB₂ and CB₁ receptors cloned in CHO cells, respectively; CB₂-agonist activity was demonstrated by its ability to inhibit forskolin-stimulated cAMP production in CB₂-transfected CHO cells (IC₅₀ = 2.7 nM). *In vivo*, compound was effective in a delayed-type hypersensitivity (DTH) assay in mice sensitized with sheep red blood cells (SRBC), with 45.2% inhibition at 40 mg/kg p.o. given at 1 h before and 5 h after DTH reaction induction. Potentially useful as an antiinflammatory, antiallergic, analgesic and immuno-modulating agent. Other exemplified compounds from this series of 2-imino-1,3-thiazine derivatives include the following:



Compound	R1	R2	A	Formula
303123	H	H	S	C ₁₇ H ₂₄ N ₂ S ₃
303126	Me	Me	O	C ₁₉ H ₂₈ N ₂ OS ₂
303128	H	Me	S	C ₁₈ H ₂₆ N ₂ S ₃

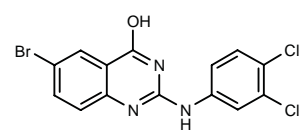
SOURCE – Shionogi.

REFERENCES

1. Hanasaki, K. et al. (Shionogi & Co. Ltd.) *2-Imino-1,3-thiazine derivs*. WO 0119807.

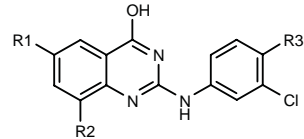
303218

6-Bromo-2-(3,4-dichlorophenylamino)quinazolin-4-ol



C14 H8 Br Cl2 N3 O; Mol wt: 385.0472

ACTION – Caspase 3 inhibitor, claimed to be useful for reducing excessive apoptosis and for the treatment of immune, proliferative and degenerative diseases such as AIDS, autoimmune diseases, pathogenic infections, cardiovascular and neurological injury, alopecia, aging, cancer, Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke, vascular dementia, head trauma, amyotrophic lateral sclerosis, neuromuscular disease, myocardial ischemia, cardiomyopathy, macular degeneration, osteoarthritis, diabetes, acute liver failure and spinal cord injury. Other exemplified compounds from this series of quinazoline derivatives include the following:



Compound	R1	R2	R3	Formula
303219	Cl	SO2N(Me)CH2CH2Ph	Cl	C ₂₃ H ₁₉ Cl ₃ N ₄ O ₃ S
303220	F	I	Cl	C ₁₄ H ₇ Cl ₂ FIN ₃ O
303221	NO2	5-Me-2-(1-pyrrolyl)-PhNHCO	Cl	C ₂₆ H ₁₈ Cl ₂ N ₆ O ₄
303222	NO2	4-(5-MeO-2-pyrimidinyl-NHSO2)-PhNHCO	Cl	C ₂₆ H ₁₈ Cl ₂ N ₈ O ₇ S
303223	NO2	4-F-PhNHCO	Me	C ₂₂ H ₁₅ ClFN ₅ O ₄
303224	NO2	3-F-5-CF3-PhCH2NHCO	Cl	C ₂₃ H ₁₃ Cl ₂ F ₄ N ₅ O ₄
303225	NO2	2-Pyr-CH=CH	Cl	C ₂₁ H ₁₃ Cl ₂ N ₅ O ₃
303226	NO2	2-Me-PhCH2NHCOCH2CH2	Cl	C ₂₅ H ₂₁ Cl ₂ N ₅ O ₄

SOURCE – AstraZeneca.

REFERENCES

1. Jacobs, R.T. et al. (AstraZeneca AB;AstraZeneca plc) *Therapeutic quinazoline cpds*. WO 0121598.

3. Bhagwat, S. *Drug discovery process using a focused kinase inhibitor library*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 318.

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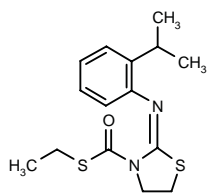
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*Identified compound **301539** Drug Data Rep 2001, 023(07): 0694.

IMMUNOMODULATING AGENTS

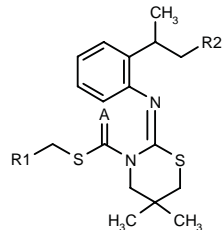
303120

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C15 H20 N2 O S2; Mol wt: 308.4680

ACTION – High-affinity cannabinoid CB₂ receptor ligand, as demonstrated by K_i values of 9 and > 5000 nM against [³H]-CP-55940 binding to human CB₂ and CB₁ receptors cloned in CHO cells, respectively; CB₂-agonist activity was demonstrated by its ability to inhibit forskolin-stimulated cAMP production in CB₂-transfected CHO cells (IC₅₀ = 2.7 nM). *In vivo*, compound was effective in a delayed-type hypersensitivity (DTH) assay in mice sensitized with sheep red blood cells (SRBC), with 45.2% inhibition at 40 mg/kg p.o. given at 1 h before and 5 h after DTH reaction induction. Potentially useful as an antiinflammatory, antiallergic, analgesic and immuno-modulating agent. Other exemplified compounds from this series of 2-imino-1,3-thiazine derivatives include the following:



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303128	H	Me	S	C ₁₈ H ₂₆ N ₂ S ₃

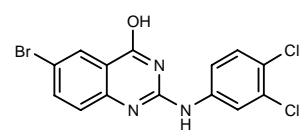
SOURCE – Shionogi.

REFERENCES

1. Hanasaki, K. et al. (Shionogi & Co. Ltd.) *2-Imino-1,3-thiazine derivs*. WO 0119807.

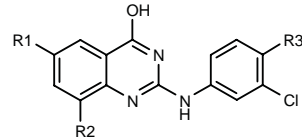
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303220	F	I	Cl	C ₁₄ H ₇ Cl ₂ FIN ₃ O
303221	NO2	5-Me-2-(1-pyrrolyl)-PhNHCO	Cl	C ₂₆ H ₁₈ Cl ₂ N ₆ O ₄
303222	NO2	4-(5-MeO-2-pyrimidinyl-NHSO2)-PhNHCO	Cl	C ₂₆ H ₁₈ Cl ₂ N ₈ O ₇ S
303223	NO2	4-F-PhNHCO	Me	C ₂₂ H ₁₅ ClFN ₅ O ₄
303224	NO2	3-F-5-CF3-PhCH2NHCO	Cl	C ₂₃ H ₁₃ Cl ₂ F ₄ N ₅ O ₄
303225	NO2	2-Pyr-CH=CH	Cl	C ₂₁ H ₁₃ Cl ₂ N ₅ O ₃
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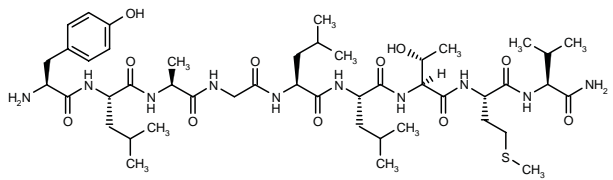
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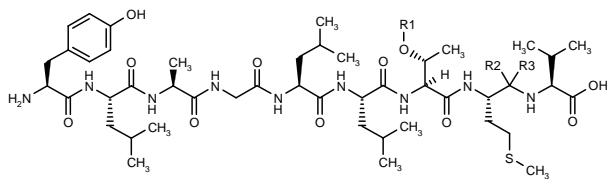
305293

L-Tyrosyl-L-leucyl-L-alanyl-glycyl-L-leucyl-L-leucyl-L-threonyl-L-methionyl-L-valinamide



C46 H78 N10 O11 S; Mol wt: 979.2472

ACTION – Immunotherapeutic agent for the treatment of Epstein-Barr virus (EBV)-associated tumors comprising an analogue of an EBV epitope derived from the membrane protein LMP2 with high affinity for HLA-A2 molecules and able to efficiently stimulate cytotoxic T-lymphocyte (CTL) responses in peripheral blood lymphocytes derived from EBV-seropositive donors. Other related peptides are:



Compound	R1	R2	R3	Formula
305402	H	H	H	C ₄₆ H ₇₉ N ₉ O ₁₁ S
305404	β-D-glucopyranosyl	-O-		C ₅₂ H ₈₇ N ₉ O ₁₇ S

SOURCE – Università di Ferrara, Ferrara (IT).

REFERENCES

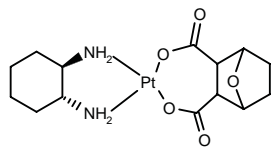
1. Marastoni, M. et al. *Peptide analogues of a subdominant epitope expressed in EBV-associated tumors: Synthesis and immunological activity.* J Med Chem 2001, 44(14): 2370.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

305288

(*trans*-Cyclohexane-1,2-diamine-κN,κN')(7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylato(2-)-κO²,κO³)platinum



C14 H22 N2 O5 Pt; Mol wt: 493.4168

ACTION – Antineoplastic agent, a combination of a modified component of a traditional Chinese medicine and a platinum complex with *in vitro* cytotoxic activity against a range of human cancer cell lines, with particular selectivity toward human liver adenocarcinoma SK-HEP-1 cells and human testicular cancer NTERA-2 cl.D1 cells (IC₅₀ = 2.97 and 0.15 μM, respectively). Compound was also active against cisplatin-resistant murine leukemia L1210 cells (IC₅₀ = 0.12 μM) and human non-small cell lung cancer NCI-H460 cells (IC₅₀ = 1.40 μM). This complex has a dual mechanism of action: inhibition of protein phosphatase PP2A and platination of DNA. In preliminary studies of the *in vivo* antitumor efficacy using human liver tumor xenografts in nude mice, the complex induced regression of tumor growth at doses that did not induce body weight loss.

SOURCES – Chinese Academy of Sciences, Beijing (CN); Chinese University of Hong Kong, Sha Tin, HK (CN).

REFERENCES

1. Au-Yeung, S.C.F. et al. (Chinese University of Hong Kong) *Synthesis of platinum complexes and uses thereof.* WO 9849174.

2. Ho, Y.-P. et al. *Potential new antitumor agents from an innovative combination of demethylcantharidin, a modified traditional Chinese medicine, with a platinum moiety.* J Med Chem 2001, 44(13): 2065.

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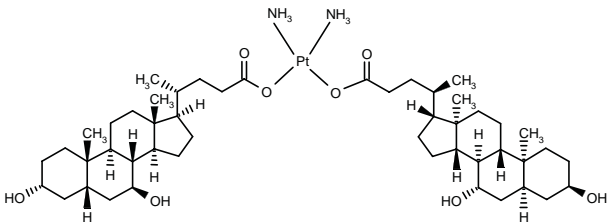
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5. Zou, J. et al. *The chiral selectivity in across-membrane transport of 1,2-diaminocyclohexane platinum(II) complexes and the contribution of leaving groups.* Chin Chem Lett 1996, 7(7): 657.

BAMET-UD2^{1,3,12}

305114

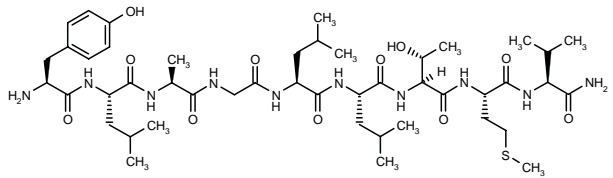
cis-[Diamminebis[(3α,5β,7β)-3,7-dihydroxycholan-24-oato-κO]]platinum



C48 H84 N2 O8 Pt; Mol wt: 1012.2780

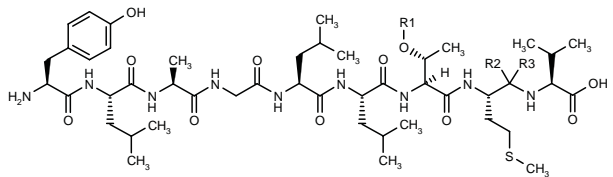
305293

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SOURCE – Università di Ferrara, Ferrara (IT).

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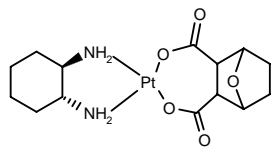
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ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

305288

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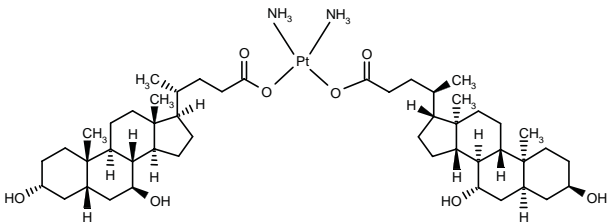
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5. Zou, J. et al. *The chiral selectivity in across-membrane transport of 1,2-diaminocyclohexane platinum(II) complexes and the contribution of leaving groups.* Chin Chem Lett 1996, 7(7): 657.

BAMET-UD2^{1,3,12}

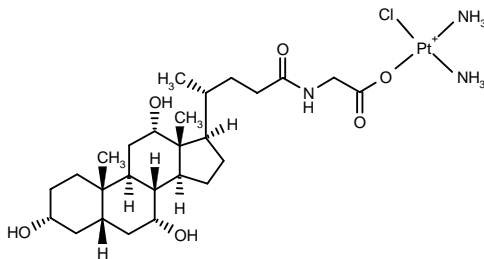
305114

cis-[Diamminebis[(3α,5β,7β)-3,7-dihydroxycholan-24-oato-κO]]platinum



C48 H84 N2 O8 Pt; Mol wt: 1012.2780

ACTION – Carrier molecule to direct a cytostatic drug to liver tumors, a complex of cisplatin and ursodeoxycholic acid that retains both the liver organotropism of the bile acid and the potent cytostatic effects of cisplatin. The antitumor effects and toxicity of the complex and cisplatin were compared in nude mice bearing murine hepatoma Hepa 1-6 orthotopically implanted in the liver. Compound was more effective than cisplatin in prolonging life span and showed a T/C value of 142% at a dose of 15 nmol/g i.p., compared with a T/C of 96% at the same dose of cisplatin. Both BAMET-UD2 and cisplatin inhibited tumor growth to the same extent and a significant beneficial effect on metastases and ascites was seen with compound, but not with cisplatin. The amount of complex in the liver was 7-fold higher than cisplatin, whereas a significantly higher concentration of cisplatin was found in the kidneys, other tissues and serum. Unlike cisplatin, the complex did not induce significant bone marrow toxicity, nephrotoxicity or neurotoxicity. Another related complex is:



Bamet-R2 [305115]^[2,4-11,13-16]: C26 H48 Cl N3 O6 Pt

SOURCE – Universidad de Salamanca, Salamanca (ES).

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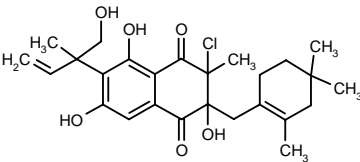
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ANTIBIOTICS AND ALKALOIDS

NK-34944

302105

3-Chloro-2,5,7-trihydroxy-6-[1-(hydroxymethyl)-1-methyl-2-propenyl]-3-methyl-2-(2,4,4-trimethyl-1-cyclohexen-1-ylmethyl)-1,2,3,4-tetrahydronaphthalene-1,4-dione



C26 H33 Cl O6; Mol wt: 476.9937

ACTION – Antineoplastic agent isolated from *Streptomyces* sp. NA-34944 (FERM P-17442), proven to inhibit the proliferation of murine leukemia J774.1 cells with an IC₅₀ value of 1.9 µg/ml.

SOURCE – Nippon Kayaku.

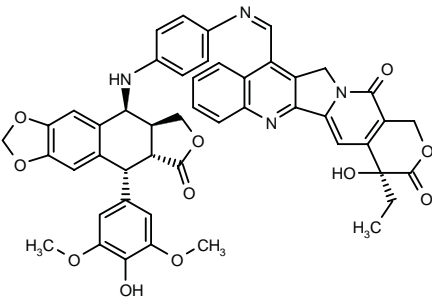
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DNA-INTERCALATING DRUGS

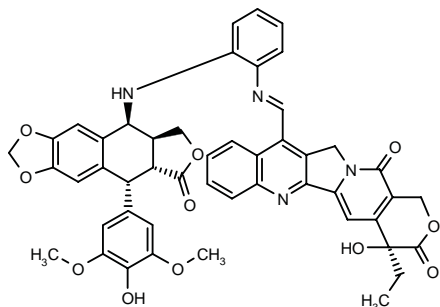
302288

4(S)-Ethyl-4-hydroxy-11-[4-[(5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-8-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-ylamino]phenyliminomethyl]-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione



C48 H40 N4 O11; Mol wt: 848.8610

ACTION – Antineoplastic agent proven active *in vivo* in nude mice bearing s.c.-implanted KB cells. Another compound from this series of covalent conjugates of topoisomerase I and topoisomerase II inhibitors is:



302289: C₄₈ H₄₀ N₄ O₁₁

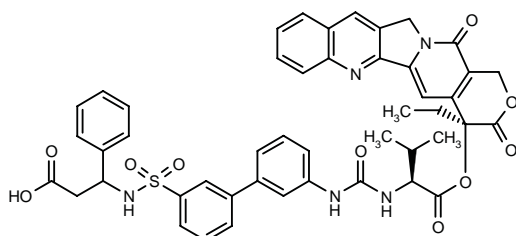
SOURCES – University of North Carolina, Chapel Hill, NC (US); Yale University, New Haven, CT (US).

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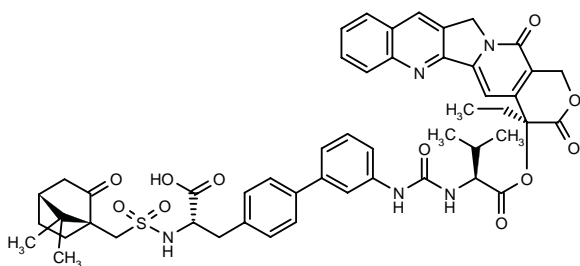
302418

3-[3'-[3-[1(*S*)-[4(*S*)-Ethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-4-yloxy-carbonyl]-2-methylpropyl]ureido]biphenyl-3-ylsulfon-amido]-3-phenylpropionic acid

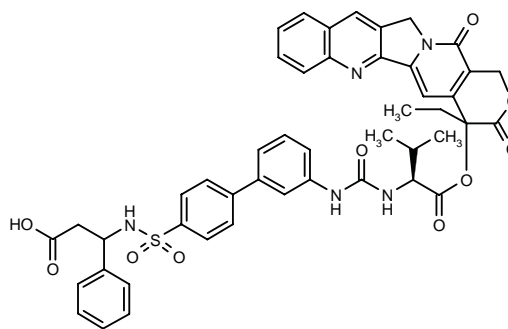


C₄₇ H₄₃ N₅ O₁₀ S; Mol wt: 869.9477

ACTION – Antineoplastic agent, a representative compound from a series of conjugates of cytostatic agents with nonpeptide $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor antagonists through a linking unit which is enzymatically or hydrolytically cleavable with release of the cytostatic. Compound was shown to inhibit binding to the $\alpha_v\beta_3$ receptor *in vitro* with an IC₅₀ value of 97 nM. In addition, it inhibited the growth of human colon adenocarcinoma SW480 and HT-29, murine melanoma B16F10 and human breast cancer BT-20, MCF-7 and MDA-MB-231 cells with respective IC₅₀ values of 15, 15, 20, 5, 10 and 20 nM. Other exemplified compounds include the following:



302419: C₅₁ H₅₃ N₅ O₁₁ S



302420: C₄₇ H₄₃ N₅ O₁₀ S

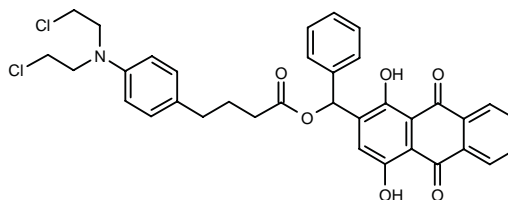
SOURCE – Bayer.

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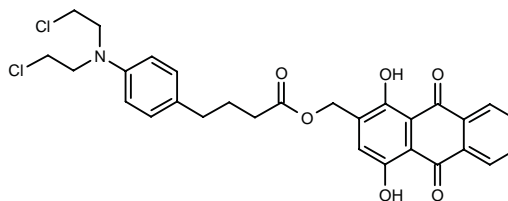
305590

4-[4-[*N,N*-Bis(2-chloroethyl)amino]phenyl]butyric acid 1-(1,4-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-phenylmethyl ester



C₃₅ H₃₁ Cl₂ N₂ O₆; Mol wt: 632.5369

ACTION – Antineoplastic agent, a chlorambucil ester with *in vitro* cytotoxic activity against murine lymphocytic leukemia L1210 cells (EC₅₀ = 1.5 µg/ml) and *in vivo* antitumor activity in mice bearing ascitic S-180 tumors. In this model, the survival rate measured 50 days after treatment was 50% on title compound (9.5 µmol/kg/day i.p. for 7 days) compared to 25% on chlorambucil. Another related compound is:



305588: C₂₉ H₂₇ Cl₂ N₂ O₆

SOURCES – Chungnam National University, Taejeon (KR); Yanbian University, Yanji (CN).

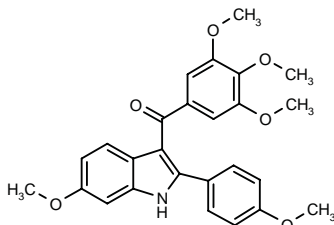
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ANTIMITOTIC DRUGS

302680

1-[6-Methoxy-2-(4-methoxyphenyl)-1*H*-indol-3-yl]-1-(3,4,5-trimethoxyphenyl)methanone



C26 H25 N O6; Mol wt: 447.4845

ACTION – Antineoplastic agent that acts by inhibiting tubulin polymerization (IC_{50} = 0.5-1.5 μ M using purified tubulin obtained from bovine brain cells). *In vitro*, compound exhibited potent cytotoxicity against murine leukemia P388 (ED_{50} = 0.0133 μ g/ml), as well as against several human cancer cell lines including pancreatic cancer BxPC-3 (GI_{50} = 0.0020 μ g/ml), ovarian cancer OVCAR-3 (GI_{50} = 0.0024 μ g/ml), CNS cancer SF-295 (GI_{50} = 0.0024 μ g/ml), non-small cell lung cancer NCI-H460 (GI_{50} = 0.0026 μ g/ml), colon cancer KM20L2 (GI_{50} = 0.0017 μ g/ml) and prostate cancer DU 145 (GI_{50} = 0.0023 μ g/ml). A representative compound from a series of trimethoxyphenyl-substituted indole derivatives and combretastatin A-4 analogues.

SOURCE – Baylor University, Waco, TX (US).

REFERENCES

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ER-086526¹⁻⁷

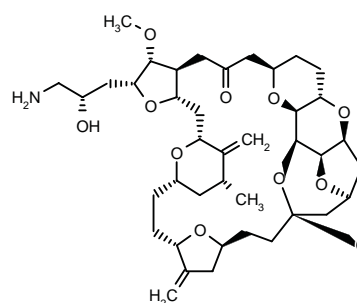
287199

(1*S*,3*S*,6*S*,9*S*,12*S*,14*R*,16*R*,18*S*,20*R*,21*R*,22*S*,26*R*,29*S*,31*R*,32*S*,35*R*,36*S*)-20-[3-Amino-2(*S*)-hydroxypropyl]-21-methoxy-14-methyl-8,15-dimethylene-2,19,30,34,37,39,40,41-octaoxanonacyclo[24.9.2.1^{3,32}.1^{3,33}.1^{6,9}.1^{12,16}.0^{18,22}.0^{29,36}.0^{31,35}]hentetracontan-24-one

(2*R*,3*R*,3*aS*,7*R*,8*aS*,9*S*,10*aR*,11*S*,12*R*,13*aR*,13*bS*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29*aS*)-2-[3-Amino-2(*S*)-hydroxypropyl]-3-methoxy-26-methyl-20,27-bis(methylene)-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methanoperhydro-9*H*,15*H*-furo[3,2-*i*]furo-[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5-one

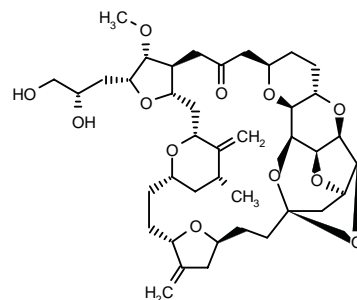
B-1939

NSC-707389



C40 H59 N O11; Mol wt: 729.9021

ACTION – Antineoplastic agent, an analogue of halicondrin B with broad-spectrum growth-inhibitory activity against a panel of human cancer cell lines including breast cancer MDA-MB-435, colon adenocarcinoma COLO 205 and DLD-1, prostate carcinoma DU 145 and LNCaP, melanoma LOX, promyelocytic leukemia HL-60 and histiocytic lymphoma U-937 (IC_{50} = 0.09, 0.71, 9.5, 0.91, 0.50, 1.4, 0.9 and 0.43 nM, respectively). Compound induced G2/M phase cell cycle arrest, disruption of mitotic spindles and inhibition of tubulin polymerization, consistent with antimitotic activity. *In vivo*, it showed strong activity against several human tumor xenografts in nude mice including breast cancer MDA-MB-435, colon adenocarcinoma COLO 205, melanoma LOX and ovarian cancer OVCAR-3 at doses of 0.05-1 mg/kg i.v. In all models, compound was more effective than paclitaxel and showed a significantly wider therapeutic window. Another synthetic macrocyclic ketone is:



ER-076349 [287198]:^{1,3-7} C40 H58 O12

B-1794

NSC-707390

SOURCE – Eisai.

REFERENCES

1. Littlefield, B.A. et al. (Eisai Co., Ltd.) *Macrocyclic analogs and methods of their use and preparation*. US 6214865, WO 9965894.

2. Dabydeen, D. et al. *The antitumor halichondrin B synthetic analog, ER-086526, is a competitive inhibitor of vinblastine binding to tubulin*. Fr-Am Colloq Cytoskelet Hum Dis (April 17-20, Marseille) 2001, Abst PA11.

3. Towle M.J. et al. *In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B*. Cancer Res 2001, 61(3): 1013.

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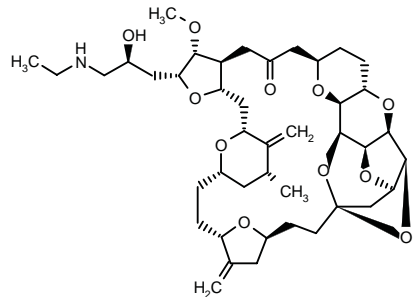
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ER-803869

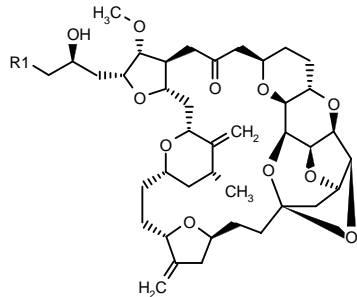
302957

(1*S*,3*S*,6*S*,9*S*,12*S*,14*R*,16*R*,18*S*,20*R*,21*R*,22*S*,26*R*,29*S*,31*R*,32*S*,35*R*,36*S*)-20-[3-(Ethylamino)-2(*S*)-hydroxypropyl]-21-methoxy-14-methyl-8,15-dimethylene-2,19,30,34,37,39,40,41-octaoxanonacyclo[24.9.2.1^{3,32}.1^{3,33}.1^{6,9}.1^{12,16}.0^{18,22}.0^{29,36}.0^{31,35}]hentetracontan-24-one



C42 H63 N O11; Mol wt: 757.9557

ACTION – Antimitotic agent proven to inhibit the growth of human colon carcinoma DLD-1 cells with an IC₅₀ value of 4.13 ± 0.64 nM. Compound exhibited potent and irreversible antimitotic activity in human histiocytic lymphoma U-937 cells, completely blocking mitosis at 3 nM at both 0 and 10 h after its removal. Other exemplified compounds from this series of halichondrin analogues include the following:



Compound	R1	Formula
ER-803851 [302958]	2(S)-(HOCH2)-1-pyrrolidiny	C ₄₆ H ₆₇ NO ₁₂
ER-803868 [302959]	4-morpholinyl	C ₄₄ H ₆₅ NO ₁₂

SOURCE – Eisai.

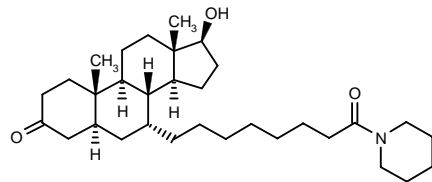
REFERENCES

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HORMONAL AGENTS

302103

(5α,7α,17β)-17-Hydroxy-7-[8-oxo-8-(1-piperidinyloctyl]-androstan-3-one



C32 H53 N O3; Mol wt: 499.7747

ACTION – Androgen receptor antagonist, as demonstrated by an IC₅₀ value of 37 nM in a dual luciferase reporter gene assay using HeLa cells transfected with a human androgen receptor expression vector. Potentially useful for the treatment or prevention of diseases such as prostate cancer, prostatic hypertrophy and male pattern baldness, as well as sexual prematurity, acne, seborrhea and hypertrichosis. A representative compound from a series of androstane derivatives having various substituents at the 7- or 11-position.

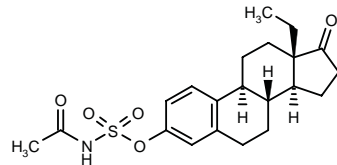
SOURCE – Chugai.

REFERENCES

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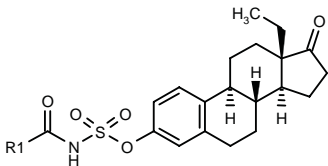
302458

N-Acetylsulfamic acid 17-oxo-18a-homoestra-1,3,5(10)-trien-3-yl ester



C21 H27 N O5 S; Mol wt: 405.5123

ACTION – Inhibitor of the activity of steroid sulfatases that does not exhibit any estrogenic activity. This compound is expected to be useful for the treatment of estrogen-dependent tumors. Other exemplified estra-1,3,5(10)-trien-3-ylsulfamates are:



Compound	R1	Formula
302459	Et	C ₂₂ H ₂₉ NO ₅ S
302460	C17H35	C ₃₇ H ₅₉ NO ₅ S
302462	Ph	C ₂₆ H ₂₉ NO ₅ S
302701	CF3	C ₂₁ H ₂₄ F ₃ NO ₅ S
302702	cyclopentyl	C ₂₅ H ₃₃ NO ₅ S

SOURCE – Jenapharm.

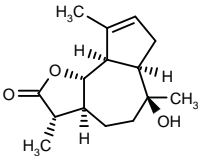
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304958

(3*S*,3*aS*,6*S*,6*aR*,9*aR*,9*bS*)-6-Hydroxy-3,6,9-trimethyl-2,3,3*a*,4,5,6,6*a*,7,9*a*,9*b*-decahydroazuleno[4,5-*b*]furan-2-one

10-Epi-8-deoxy-11β*H*,13-dihydrocumambrin B



C15 H22 O3; Mol wt: 250.3358

ACTION – Aromatase inhibitor with *K_i* values of 1.5 and 36 μM for enzyme inhibition in human placental microsomes and human choriocarcinoma JEG-3 cells, respectively. Compared to the clinically available aminoglutethimide, compound showed similar aromatase-inhibitory activity but did not affect the cholesterol side-chain cleavage activity (P450scc) of human placental mitochondria. *In vivo*, both compound and aminoglutethimide (70 mg/kg/day p.o.) inhibited androstenedione-induced uterine hypertrophy in sexually immature mice (41 and 54%, respectively). Potentially useful for the treatment of breast cancer.

SOURCE – Universidad Nacional de Córdoba, Córdoba (AR).

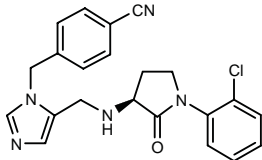
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

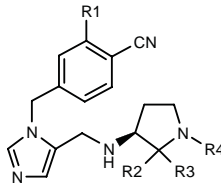
302596

4-[5-[1-(2-Chlorophenyl)-2-oxopyrrolidin-3(*S*)-ylamino-methyl]-1*H*-imidazol-1-ylmethyl]benzonitrile



C22 H20 Cl N5 O; Mol wt: 405.8870

ACTION – An inhibitor of protein prenyltransferases, particularly protein farnesyltransferase, and the prenylation of the oncogene protein Ras, with potential in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, as well as for conferring radiation sensitivity to tumor cells. Other specifically claimed 5-membered nitrogen-containing heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
302598	OPh	-O-		3-Cl-PhCH2	C ₂₉ H ₂₆ ClN ₅ O ₂
302599	OMe	-O-		3-Cl-PhCH2	C ₂₄ H ₂₄ ClN ₅ O ₂
302600	H	-O-		3-Cl-PhCH2	C ₂₉ H ₃₃ ClN ₅ O ₂
302601	F	-O-		3-Cl-PhCH(3-OH-Ph)	C ₂₉ H ₂₅ ClFN ₅ O ₂
302602	H	H	H	2-EtS-3-Pyr-CO	C ₂₄ H ₂₆ N ₆ OS
302603	H	H	H	1-adamantyl-CH2CO	C ₂₈ H ₃₈ N ₅ O

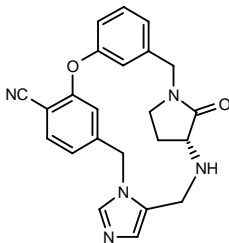
SOURCE – Merck & Co.

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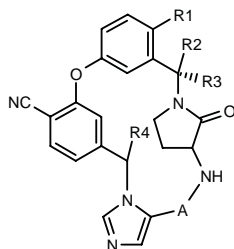
302604

(6*R*)-27-Oxo-20-oxa-3,7,11,13-tetraazapentacyclo-[19.3.1.1^{3,6}.1^{15,19}.0^{9,13}]heptacos-1(25),9,11,15(26),16,18,21,23-octaene-18-carbonitrile

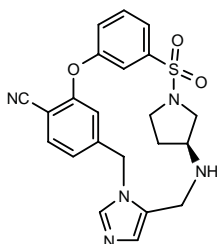


C23 H21 N5 O2; Mol wt: 399.4519

ACTION – An inhibitor of protein prenyltransferases, particularly protein farnesyltransferase, and the prenylation of the oncogene protein Ras, with potential in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, as well as for conferring radiation sensitivity to tumor cells. Other specifically claimed macrocyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Isomer	Formula
302606		-CH=CHCH=		H	-CH2-	S	C ₂₆ H ₂₁ N ₅ O ₂
302607		-(CH ₂) ₃ -	H	H	-CH2-	R	C ₂₆ H ₂₆ N ₅ O ₂
302608	H	H	H	(S)-Me	-CH2-	R	C ₂₄ H ₂₃ N ₅ O ₂
302610	H	H	H	(R)-Me	-CH2-	R	C ₂₄ H ₂₃ N ₅ O ₂
302611		-CH=CHCH=		H	-(CH ₂) ₂ -	S	C ₂₇ H ₂₃ N ₅ O ₂
302612		-CH=CHCH=		H	-(CH ₂) ₂ -	R	C ₂₇ H ₂₃ N ₅ O ₂
302614		-(CH ₂) ₂ -	H	H	-CH2-	R	C ₂₅ H ₂₃ N ₅ O ₂
302615		-OCH ₂ CH ₂ -	H	H	-CH2-	R	C ₂₅ H ₂₃ N ₅ O ₃



302605: C₂₂ H₂₁ N₅ O₃ S

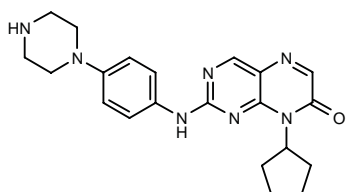
SOURCE – Merck & Co.

REFERENCES

1. Bell, I.M. et al. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 0118006.

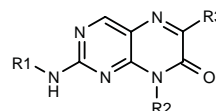
302734

8-Cyclopentyl-2-[4-(1-piperazinyl)phenylamino]pteridin-7(8H)-one



C₂₁ H₂₅ N₇ O; Mol wt: 391.4765

ACTION – A representative compound from a series of inhibitors of cyclin-dependent serine/threonine kinases (CDKs), Wee 1 tyrosine kinase and growth factor-mediated tyrosine kinases, with IC₅₀ values of 0.007, 0.18, 0.75, 0.61 and 3.3 μM, respectively, against CDK4d, CDK2a, CDK1b, CDK2e and c-Src. Potentially useful for the treatment of cancer, atherosclerosis, restenosis, angiogenesis, viral and fungal infections, type 1 diabetes, multiple sclerosis, glomerulonephritis, neurodegenerative diseases, autoimmune diseases, transplant rejection and inflammation. Other exemplified compounds from this series of 8H-pteridin-7-ones, tetrahydropteridin-7-ones, 5H,8H-pteridine-6,7-diones and pteridin-7-ureas include the following:



Compound	R1	R2	R3	Formula
302735	4-(4-morpholinyl)-Ph	Me	2,6-(Cl) ₂ -Ph	C ₂₃ H ₂₀ Cl ₂ N ₆ O ₂
302736	4-[N(Et) ₂ CH ₂ CH ₂ O]-Ph	Me	2,6-(Cl) ₂ -Ph	C ₂₅ H ₂₆ Cl ₂ N ₆ O ₂
302737	4-[CON(Et) ₂]-Ph	Me	2,6-(Cl) ₂ -Ph	C ₂₄ H ₂₂ Cl ₂ N ₆ O ₂
302738	4-(4-morpholinyl)-Ph	cyclopentyl	H	C ₂₁ H ₂₄ N ₆ O ₂
302739	4-(4-Me-1-Piz)-Ph	cyclopentyl	H	C ₂₂ H ₂₇ N ₇ O
302740	4-(4-Me-1-Piz)-Ph	cyclopentyl	Me	C ₂₃ H ₂₉ N ₇ O
302741	4-Pyr	cyclopentyl	H	C ₁₆ H ₁₆ N ₆ O
302743	4-(3-NH ₂ -1-pyrrolidinyl)-Ph	cyclopentyl	H	C ₂₁ H ₂₅ N ₇ O

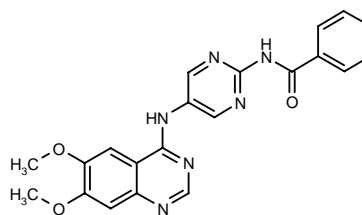
SOURCE – Pfizer.

REFERENCES

1. Denny, W.A. et al. (Pfizer Inc.) *Pteridinones as kinase inhibitors*. WO 0119825.

303152

N-[5-(6,7-Dimethoxyquinazolin-4-ylamino)pyrimidin-2-yl]benzamide



C₂₁ H₁₈ N₆ O₃; Mol wt: 402.4122

ACTION – Agent for the treatment of proliferative disorders such as cancer, particularly colorectal and breast cancer, an inhibitor of aurora2 kinase (IC₅₀ = 0.00785 μM). Compound was shown to inhibit the proliferation of human breast cancer MCF-7 cells with an IC₅₀ value of 1.7 μM and to inhibit the incorporation of 5'-bromo-2'-deoxyuridine (BrdU) into cellular DNA of MCF-7 cells with an IC₅₀ value in the range 1.92-2.848 μM. In addition, it was shown to arrest the cell cycle in the G₂ phase following treatment of MCF-7 cells with 10 μM (30.38% of cells in G₂/M vs. 5.97% in controls). A representative compound from a series of quinazoline derivatives.

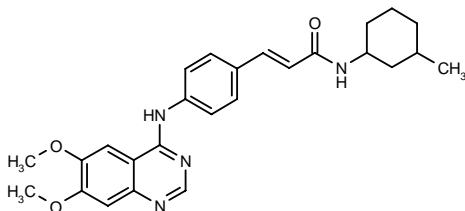
SOURCE – AstraZeneca.

REFERENCES

1. Mortlock, A.A. and Keen, N.J. (AstraZeneca AB;AstraZeneca plc) *Therapeutic quinazoline derivs.* WO 0121597.

303154

3-[4-(6,7-Dimethoxyquinazolin-4-ylamino)phenyl]-N-(3-methylcyclohexyl)-2-propenamide



C26 H30 N4 O3; Mol wt: 446.5480

ACTION – Agent for the treatment of proliferative disorders such as cancer, particularly colorectal and breast cancer, an inhibitor of aurora2 kinase (IC_{50} = 0.117 μ M). Compound was shown to inhibit the proliferation of human breast cancer MCF-7 cells with an IC_{50} value of 6.38 μ M and to inhibit the incorporation of 5'-bromo-2'-deoxyuridine (BrdU) into cellular DNA of MCF-7 cells with an IC_{50} value of 2.47 μ M. In addition, it was shown to arrest the cell cycle in the G2 phase following treatment of MCF-7 cells with 12.76 μ M (49.62% of cells in G2/M vs. 9.81% in controls). A representative compound from a series of quinazoline derivatives.

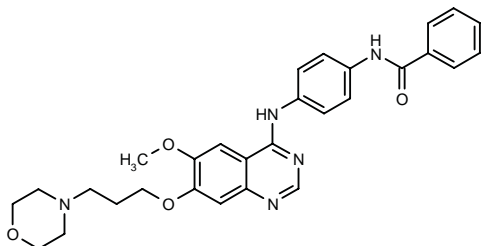
SOURCE – AstraZeneca.

REFERENCES

1. Mortlock, A.A. and Keen, N.J. (AstraZeneca AB;AstraZeneca plc) *Quinazoline derivs.* WO 0121595.

303155

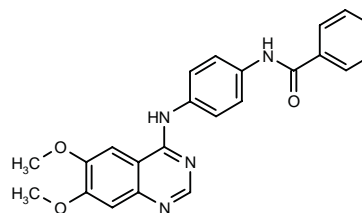
N-[4-[6-Methoxy-7-[3-(4-morpholinyl)propoxy]quinazolin-4-ylamino]phenyl]benzamide



C29 H31 N5 O4; Mol wt: 513.5949

ACTION – Agent for the treatment of proliferative disorders such as cancer, particularly colorectal and breast cancer, an inhibitor of aurora2 kinase (IC_{50} = 0.0193 μ M). Compound was shown to inhibit the proliferation of human breast cancer MCF-7 cells with an IC_{50} value of 1.06 μ M and to inhibit the incorporation of 5'-bromo-2'-deoxyuridine (BrdU) into cellular DNA of MCF-7 cells with an IC_{50} value in the range 0.159-0.209 μ M. In addition, it was shown to arrest the cell cycle in the G2 phase following treatment of MCF-7 cells with 2.12 μ M

(68.21% of cells in G2/M vs. 10.55% in controls). Another exemplified compounds from this series of quinazoline derivatives is:



303157: C23 H20 N4 O3

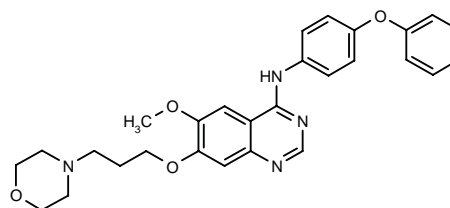
SOURCE – AstraZeneca.

REFERENCES

1. Mortlock, A.A. et al. (AstraZeneca AB;AstraZeneca plc) *Quinazoline derivs. and their use as pharmaceuticals.* WO 0121596.

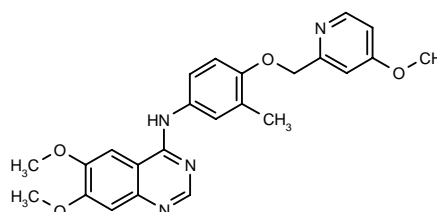
303158

6-Methoxy-7-[3-(4-morpholinyl)propoxy]-N-(4-phenoxyphenyl)quinazolin-4-amine



C28 H30 N4 O4; Mol wt: 486.5690

ACTION – Agent for the treatment of proliferative disorders such as cancer, particularly colorectal and breast cancer, an inhibitor of aurora2 kinase (IC_{50} = 0.069 μ M). Compound was shown to inhibit the proliferation of human breast cancer MCF-7 cells with an IC_{50} value of 2.89 μ M and to inhibit the incorporation of 5'-bromo-2'-deoxyuridine (BrdU) into cellular DNA of MCF-7 cells with an IC_{50} value of 3.68 μ M. In addition, it was shown to arrest the cell cycle in the G2 phase following treatment of MCF-7 cells with 5.78 μ M (28.97% of cells in G2/M vs. 8.15% in controls). Another exemplified compound from this series of quinazoline derivatives is:



303159: C24 H24 N4 O4

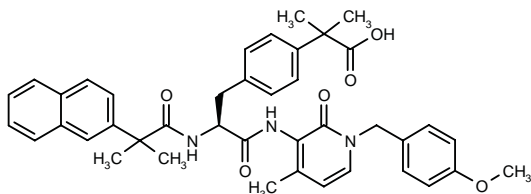
SOURCE – AstraZeneca.

REFERENCES

1. Mortlock, A.A. and Keen, N.J. (AstraZeneca AB;AstraZeneca plc) *Quinazoline cpds. and pharmaceutical compns. containing them.* WO 0121594.

305377

2-[4-[2(S)-[N-[1-(4-Methoxybenzyl)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]carbamoyl]-2-[2-methyl-2-(2-naphthyl)propionamido]ethyl]phenyl]-2-methylpropionic acid



C41 H43 N3 O6; Mol wt: 673.8057

ACTION – Nonpeptide ligand for the SH2 domain of the Src protein tyrosine kinase p56^{lck} ($K_d = 1 \mu\text{M}$) with good cell permeation properties. Compound inhibited the early events of T-cell signal transduction via inhibition of Ca^{2+} influx. Consequently, it inhibited IL-2 production from CD4+ T-cells ($\text{EC}_{50} = 9.4 \mu\text{M}$) and CD4+ T-cell proliferation ($\text{EC}_{50} = 8.7 \mu\text{M}$). Potentially useful as an immunosuppressive agents, as well as for the treatment or prevention of neoplastic and chronic inflammatory disorders.

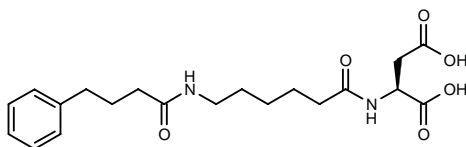
SOURCE – Boehringer Ingelheim.

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1. Betageri, R. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Pyridones as Src family SH2 domain inhibitors*. EP 1045836, US 6054470, US 6156784, WO 9931066.
2. Proudfoot, J.R. et al. *Nonpeptidic, monocharged, cell permeable ligands of the p56lck SH2 domain*. J Med Chem 2001, 44(15): 2421.

TR-060**303141**

N-[6-(4-Phenylbutyramido)hexanoyl]-L-aspartic acid



C20 H28 N2 O6; Mol wt: 392.4492

ACTION – An inhibitor of prenylated pyrophosphate-consuming enzymes such as protein farnesyltransferase ($\text{IC}_{50} = 304 \mu\text{M}$), protein geranylgeranyltransferase and several other enzymes involved in the biosynthesis of terpenes such as farnesyl pyrophosphate synthase, squalene synthase and geranylgeranyl pyrophosphate synthase, with potential for the treatment of cancer, restenosis, atherosclerosis and osteoporosis, as well as for lowering cholesterol levels.

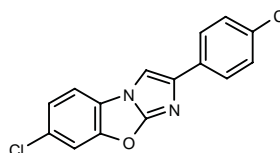
SOURCES – Universiteit Leiden, Leiden (NL); Nederlandse Centrale Organisatie TNO, The Hague (NL).

REFERENCES

1. Burm, B.E.A. et al. (Universiteit Leiden; Nederlandse Centrale Organisatie TNO) *Novel inhibitors of prenylated pyrophosphate consuming enzymes*. EP 1090909, JP 2001158799.

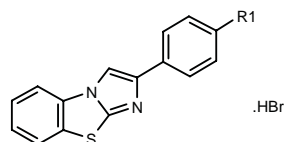
ANGIOGENESIS INHIBITORS**302201**

7-Chloro-2-(4-chlorophenyl)imidazo[2,1-b]benzoxazole



C15 H8 Cl2 N2 O; Mol wt: 303.1472

ACTION – Vascular endothelial growth factor (VEGF) inhibitor proven to inhibit VEGF-stimulated proliferation of human umbilical vein endothelial cells (HUVEC; $\text{IC}_{50} < 0.10 \mu\text{M}$). Potentially useful for the treatment of cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, scleroderma and ocular diseases such as neovascular glaucoma. Within this series of tricyclic heteroaryl derivatives, the following compounds are also included:



Compound	R1	Formula
302202	i-Pr	$\text{C}_{18}\text{H}_{16}\text{N}_2\text{S} \cdot \text{HBr}$
302203	N(Et)2	$\text{C}_{19}\text{H}_{19}\text{N}_3\text{S} \cdot \text{HBr}$

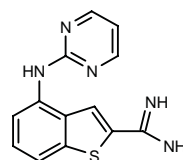
SOURCE – Yamanouchi.

REFERENCES

1. Matsuhisa, A. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Tricyclic heteroaryl derivs*. JP 2001048786.

302287

4-(Pyrimidin-2-ylamino)benzothiophene-2-carboxamidine



C13 H11 N5 S; Mol wt: 269.3309

ACTION – Urokinase inhibitor ($\text{IC}_{50} = 122 \text{ nM}$) with potential for the treatment of angiogenesis, bone restructuring, embryo implantation in the uterus, infiltration of immune cells into inflammatory sites, ovulation, spermatogenesis, tissue remodeling during wound repair and organ differentiation, fibrosis, tumor invasion and metastasis, and tissue destruction in arthritis. A specifically claimed compound from a series of benzothiophene derivatives.

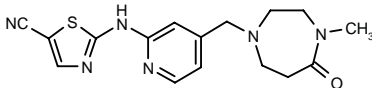
SOURCE – Abbott.

REFERENCES

1. Dellaria, J.F. Jr. (Abbott Laboratories Inc.) *Urokinase inhibitors*. US 6207701.

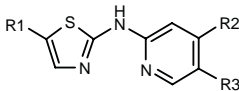
302585

2-[4-(4-Methyl-5-oxoperhydro-1,4-diazepin-1-ylmethyl)-pyridin-2-ylamino]thiazole-5-carbonitrile



C16 H18 N6 O S; Mol wt: 342.4252

ACTION – An inhibitor of tyrosine kinases such as vascular endothelial growth factor (VEGF) receptor tyrosine kinase, with potential for the treatment of cancer, angiogenesis including ocular disorders such as retinal vascularization, diabetic retinopathy and age-related macular degeneration, and inflammatory diseases such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions. Other specifically claimed nitrogen-containing heterocyclic compounds include the following:



Compound	R1	R2	R3	Formula
302586	Ph	4-(MeSO2)-1-Piz-CH2	H	C ₂₀ H ₂₃ N ₆ O ₂ S ₂
302587	CN	4-(HOCH2CO)-1-Piz-CH2	H	C ₁₆ H ₁₈ N ₆ O ₂ S
302588	CN	5-oxo-3-pyrrolidinyl-NHCH2	H	C ₁₄ H ₁₄ N ₆ OS
302589	CN	4-Me-3-oxo-1-Piz-CH2	H	C ₁₅ H ₁₆ N ₆ OS
302590	CN	1-Piz-CH2	H	C ₁₄ H ₁₆ N ₆ S
302591	Ph	4-Me-3-oxo-1-Piz-CH2	H	C ₂₀ H ₂₁ N ₆ OS
302592	Ph	H	1-Pip-(CH2)3	C ₂₂ H ₂₆ N ₄ S
302593	Ph	2-CO2H-1-Pip-CH2	H	C ₂₁ H ₂₂ N ₄ O ₂ S

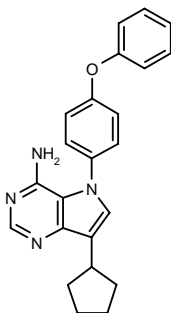
SOURCE – Merck & Co.

REFERENCES

1. Bilodeau, M.T. et al. (Merck & Co., Inc.) *Tyrosine kinase inhibitors*. WO 0117995.

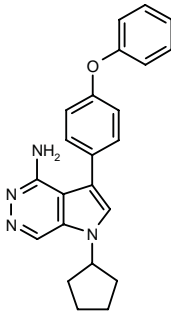
302666

7-Cyclopentyl-5-(4-phenoxyphenyl)-5H-pyrrolo[3,2-d]-pyrimidin-4-amine



C23 H22 N4 O; Mol wt: 370.4538

ACTION – An inhibitor of protein kinases, particularly tyrosine kinases involved in angiogenic and/or edematous processes such as Tie-2 tyrosine kinase, with potential for the treatment of angiogenic, hyperproliferative and immunological disorders, among others. Another exemplified compound is:



302667: C23 H22 N4 O

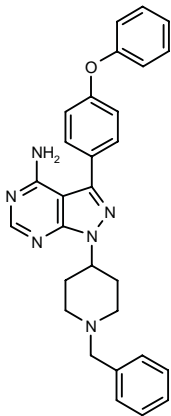
SOURCE – BASF.

REFERENCES

1. Hirst, G.C. (BASF AG) *Kinase inhibitors as therapeutic agents*. WO 0119828.

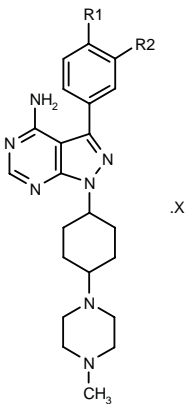
302668

1-(1-Benzylpiperidin-4-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

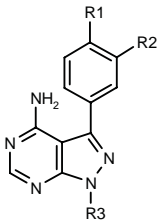


C29 H28 N6 O; Mol wt: 476.5812

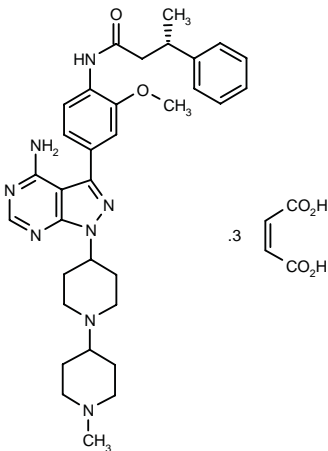
ACTION – An inhibitor of protein kinases, particularly tyrosine kinases involved in angiogenic and/or edematous processes such as Tie-2 tyrosine kinase, with potential for the treatment of angiogenic, hyperproliferative and immunological disorders, among others. Other exemplified compounds from this series of pyrazolopyrimidines include the following:



Compound	R1	R2	Isomer	X	Formula
302669	2,6-(MeO)2-Ph-CH2NH	OMe	trans	.2CH3CO2H	C ₃₂ H ₄₂ N ₈ O ₃ .2C ₂ H ₄ O ₂
302670	H	NH-CH2Ph	cis	.3CH3CO2H	C ₂₉ H ₃₆ N ₈ .3C ₂ H ₄ O ₂
302671	2-Br-Ph-CH2SO2NH	F	cis	dimaleate	C ₂₉ H ₃₄ BrFN ₈ O ₂ S .2C ₄ H ₄ O ₄
302672	CONHPh	OMe	cis		C ₃₀ H ₃₆ N ₈ O ₂
302673	NHCH(Me)Ph	H	cis	.2CH3CO2H	C ₃₀ H ₃₈ N ₈ .2C ₂ H ₄ O ₂
302675	(R)-CONH-CH2CH(Me)Ph	OMe	cis	dimaleate	C ₃₃ H ₄₂ N ₈ O ₂ .2C ₄ H ₄ O ₄



Compound	R1	R2	R3	Formula
302674	2,3-(Cl)2-Ph-SO2NH	F	CH2CONH-(CH2)3N(Me)2	C ₂₄ H ₂₅ Cl ₂ FN ₈ O ₃ S
302678	OPh	H	3-OH-3-(NH2CH2)-cyclobutyl	C ₂₂ H ₂₂ N ₆ O ₂



302677: C33 H42 N8 O2 . 3 C4 H4 O4

SOURCE – BASF.

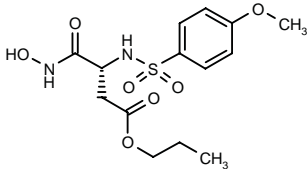
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1. Hirst, G.C. et al. (BASF AG) *Pyrazolopyrimidines as therapeutic agents*. WO 0119829.

303251

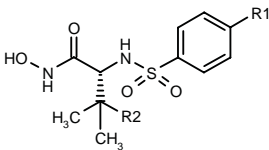
4-(Hydroxyamino)-3(R)-(4-methoxyphenylsulfonamido)-4-oxobutyric acid propyl ester

N-Hydroxy-3(R)-(4-methoxyphenylsulfonamido)-succinamic acid propyl ester

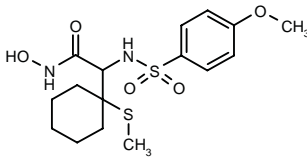


C14 H20 N2 O7 S; Mol wt: 360.3850

ACTION – An inhibitor of metalloproteases, particularly matrix metalloproteinases, with potential for the treatment of diseases mediated by excess or undesired metalloprotease activity such as cancer, osteoarthritis, rheumatoid arthritis, skin disorders, ocular disorders, cardiovascular disorders, inflammatory disorders and gum disease. Other exemplified compounds from this series of acyclic hydroxamic acids include the following:



Compound	R1	R2	Formula
303252	OMe	SMe	C ₁₃ H ₂₀ N ₂ O ₅ S ₂
303253	Br	SMe	C ₁₂ H ₁₇ BrN ₂ O ₄ S ₂
303254	OBu	SMe	C ₁₆ H ₂₆ N ₂ O ₅ S ₂
303255	OMe	4-MeO-PhCH2S	C ₂₀ H ₂₆ N ₂ O ₆ S ₂
303257	OMe	SO2Me	C ₁₃ H ₂₀ N ₂ O ₇ S ₂



303256: C16 H24 N2 O5 S2

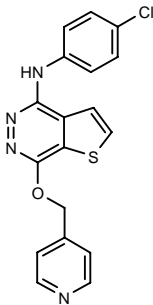
SOURCE – Procter & Gamble.

REFERENCES

1. Almstead, N.G. et al. (The Procter & Gamble Co.) *Acyclic metalloprotease inhibitors*. US 6218389.

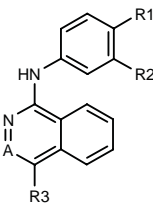
303258

N-(4-Chlorophenyl)-7-(pyridin-4-ylmethoxy)thieno[2,3-d]-pyridazin-4-amine

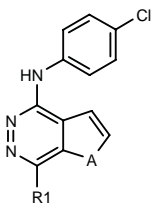


C18 H13 Cl N4 O S; Mol wt: 368.8467

ACTION – Antiangiogenic agent, an inhibitor of KDR kinase (IC₅₀ value = 100 nM or less) proven to inhibit vascular endothelial growth factor (VEGF)-induced KDR phosphorylation in NIH3T3 cells expressing KDR (IC₅₀ = 20-50 nM). *In vivo*, it was shown to inhibit angiogenesis in a mouse Matrigel model (> 60% inhibition at 100 and 300 mg/kg p.o. once daily). Potentially useful for the treatment of conditions characterized by abnormal angiogenesis or hyperpermeability processes such as tumor growth, retinopathy (e.g., diabetic retinopathy and age-related macular degeneration), rheumatoid arthritis, psoriasis or bullous disorders associated with subepidermal blister formation such as bullous pemphigoid, erythema multiforme and dermatitis herpetiformis. Other exemplified compounds from this series of substituted pyridines and pyridazines include the following:



Compound	R1	R2	R3	A	Formula
303259	-(CH2)3-		4-Pyr-S	CH	C ₂₃ H ₁₉ N ₃ S
303260	-(CH2)3-		4-Pyr-CH2	CH	C ₂₄ H ₂₁ N ₃
303265	Cl	H	1H-1,2,3-benzotriazol-6-yl-NH	N	C ₂₀ H ₁₄ ClN ₇
303266	H	Br	6-benzothiazolyl-NH	N	C ₂₁ H ₁₄ BrN ₅ S
303267	i-Pr	H	6-benzothiazolyl-NH	N	C ₂₄ H ₂₁ N ₅ S
303268	H	OMe	6-benzothiazolyl-NH	N	C ₂₂ H ₁₇ N ₅ OS
303269	Me	F	6-benzothiazolyl-NH	N	C ₂₂ H ₁₆ FN ₅ S
303270	Cl	H	6-benzothiazolyl-NH	N	C ₂₁ H ₁₄ ClN ₅ S



Compound	R1	A	Formula
303261	2-(NH2CO)-4-Pyr-CH2O	S	C ₁₉ H ₁₄ ClN ₅ O ₂ S
303262	2-(MeNHCO)-4-Pyr-CH2O	S	C ₂₀ H ₁₆ ClN ₅ O ₂ S
303263	2-(MeNHCO)-4-Pyr-CH2O	O	C ₂₀ H ₁₆ ClN ₅ O ₃
303264	6-benzothiazolyl-NH	S	C ₁₉ H ₁₂ ClN ₅ S ₂

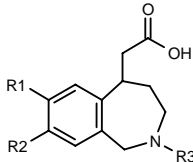
SOURCE – Bayer.

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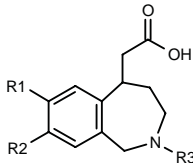
303394

2-[2-[N-[3-(Pyridin-2-ylamino)propyl]carbamoyl]-2,3,4,5-tetrahydro-1H-2-benzazepin-5-yl]acetic acid

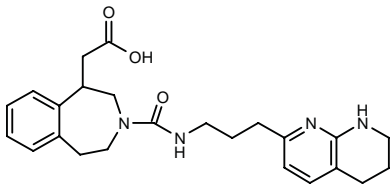


C21 H26 N4 O3; Mol wt: 382.4614

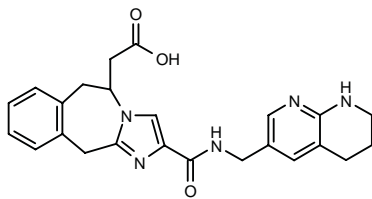
ACTION – Integrin modulator that antagonizes $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ and/or $\alpha_v\beta_6$ receptors. It inhibited cellular proliferation and/or adhesion of primary human umbilical vein endothelial cells (HUVEC) with an IC₅₀ of 30 μ M or less. This compound is potentially useful for the treatment of cancer, tumor growth and metastasis, diabetic retinopathy, macular degeneration, angiogenesis, restenosis, bone resorption, atherosclerosis, inflammation, viral infection and wound healing. Other exemplified fused cycloheptanes and azacycloheptanes include the following:



Compound	R1	R2	R3	Isomer	Formula
303395	H	H	6-(t-BuOCONH)-2-Pyr-(CH2)3NHCO		C ₂₆ H ₃₄ N ₄ O ₅
303396	H	H	2-Pyr-NH(CH2)3NHCOCH2		C ₂₂ H ₂₈ N ₄ O ₃
303400	H	H	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl-(CH2)2NHCO	R	C ₂₃ H ₂₈ N ₄ O ₃
303402	Br	Br	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl-(CH2)3NHCO		C ₂₄ H ₂₈ Br ₂ N ₄ O ₃
303403	H	F	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl-(CH2)2NHCO		C ₂₃ H ₂₇ FN ₄ O ₃



303399: C24 H30 N4 O3



303401: C24 H25 N5 O3

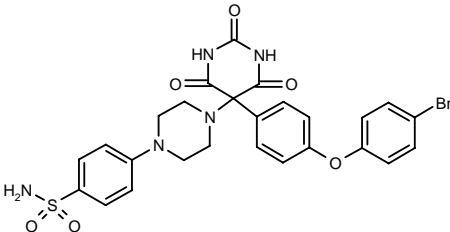
SOURCE – Amgen.

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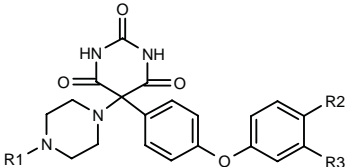
303480

4-[4-[5-[4-(4-Bromophenoxy)phenyl]-2,4,6-trioxohexahydropyrimidin-5-yl]piperazin-1-yl]benzenesulfonamide



C26 H24 Br N5 O6 S; Mol wt: 614.4746

ACTION – Antineoplastic agent, an inhibitor of matrix metalloproteinases (MMPs) such as human neutrophil collagenase (MMP-8; IC₅₀ = 2.8 nM, catalytic domain), reported to possess good oral bioavailability. Other specifically claimed compounds from this series of 5,5-disubstituted pyrimidine-2,4,6-trione derivatives are:



Compound	R1	R2	R3	Formula
303481	2-pyrimidinyl	Cl	H	C ₂₄ H ₂₁ ClN ₆ O ₄
303482	2-pyrazinyl	Cl	H	C ₂₄ H ₂₁ ClN ₆ O ₄
303483	2-pyrimidinyl	Cl	Cl	C ₂₄ H ₂₀ Cl ₂ N ₆ O ₄
303484	2-pyrazinyl	Cl	Cl	C ₂₄ H ₂₀ Cl ₂ N ₆ O ₄
303485	2-pyrimidinyl	Br	H	C ₂₄ H ₂₁ BrN ₆ O ₄
303486	4-(HOCH2CH2NHSO2)-Ph	Cl	H	C ₂₈ H ₂₆ ClN ₅ O ₇ S
303487	4-[N(Me)2CH2CH2NHSO2]-Ph	Br	H	C ₃₀ H ₃₃ BrN ₆ O ₆ S
303488	4-(NH2SO2)-Ph	Cl	H	C ₂₆ H ₂₄ ClN ₅ O ₆ S
303489	4-[N(CH2CH2OH)2SO2]-Ph	Cl	H	C ₃₀ H ₃₂ ClN ₅ O ₈ S
303490	4-[HOCH2CH(OH)CH2NHSO2]-Ph	H	H	C ₂₉ H ₃₁ N ₅ O ₈ S
303491	4-[CH(CH2OH)2NHSO2]-Ph	H	H	C ₂₉ H ₃₁ N ₅ O ₈ S
303493	4-[H(OCH2CH2)3NHSO2]-Ph	H	H	C ₃₂ H ₃₇ N ₅ O ₉ S
303495	4-[C(CH2OH)3NHSO2]-Ph	H	H	C ₃₀ H ₃₃ N ₅ O ₉ S
303496	4-[C(CH2OH)3NHSO2]-Ph	Cl	H	C ₃₀ H ₃₂ ClN ₅ O ₉ S
303497	4-(2-oxo-1,3-dioxolan-4-yl-CH2NHSO2)-Ph	H	H	C ₃₀ H ₂₉ N ₅ O ₉ S

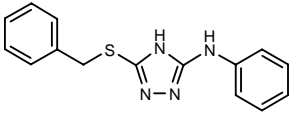
SOURCE – Roche.

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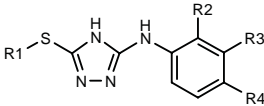
303512

5-Benzylsulfanyl-*N*-phenyl-4*H*-1,2,4-triazol-3-amine

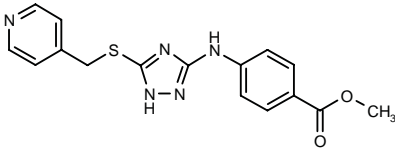


C15 H14 N4 S; Mol wt: 282.3696

ACTION – Nonpeptide reversible inhibitor of type 2 methionine aminopeptidase (MAP2), expected to be useful for inhibiting angiogenesis and for the treatment of disease conditions involving angiogenesis such as cancer, hemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	Formula
303513	CH2CH2CH(OMe)2	H	H	H	C ₁₃ H ₁₈ N ₄ O ₂ S
303514	2-F-PhCH2	H	H	Me	C ₁₆ H ₁₅ FN ₄ S
303515	5-(CO2Et)-2-furyl-CH2	Me	H	H	C ₁₇ H ₁₈ N ₄ O ₃ S
303517	cyclohexyl-CH2	Ph	H	H	C ₂₁ H ₂₄ N ₄ S
303518	CH2Ph	OMe	H	H	C ₁₆ H ₁₆ N ₄ OS
303519	2-MeO-PhCH2	i-Pr	H	H	C ₁₉ H ₂₂ N ₄ OS
303520	3-furyl	H	Me	H	C ₁₃ H ₁₂ N ₄ OS
303521	2-Cl-PhCH2	Me	H	OMe	C ₁₇ H ₁₇ ClN ₄ OS



303516: C16 H15 N5 O2 S

SOURCE – GlaxoSmithKline.

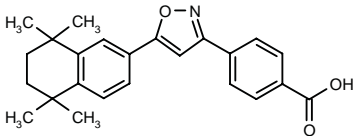
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OTHER ONCOLYTIC DRUGS

304407

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)isoxazol-3-yl]benzoic acid



C24 H25 N O3; Mol wt: 375.4655

ACTION – Retinoid receptor ligand with growth-inhibitory and apoptotic activity in human promyelocytic leukemia HL-60 cells (IC_{50} = 1 and 5 μ M, respectively), as well as in retinoic acid-resistant HL-60R, chronic myelogenous leukemia K-562 and cutaneous T-cell lymphoma HUT 78 cells (IC_{50} = 0.8-4.8 μ M). Moreover, compound showed high retinoid transactivation activity and induced differentiation in HL-60 cells, but not in the other cell lines. Potentially useful for the treatment of cancer, especially leukemia resistant to conventional treatment.

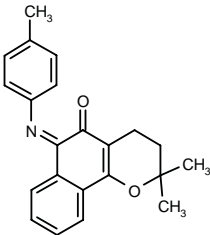
SOURCES – Università degli Studi di Bologna, Bologna (IT); Università di Ferrara, Ferrara (IT); University of Oklahoma Health Science Center, Oklahoma City, OK (US); Università degli Studi di Palermo, Palermo (IT).

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1. Simoni, D. et al. *Heterocycle-containing retinoids. Discovery of a novel isoxazole arotinoid possessing potent apoptotic activity in multidrug and drug-induced apoptosis-resistant cells.* J Med Chem 2001, 44(14): 2308.

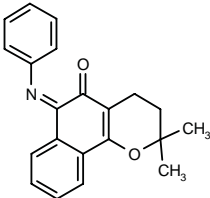
304860

2,2-Dimethyl-6(Z)-(4-methylphenylimino)-3,4,5,6-tetrahydro-2H-naphtho[1,2-b]pyran-5-one



C22 H21 N O2; Mol wt: 331.4129

ACTION – Antineoplastic agent, a β -lapachone derivative with *in vitro* cytotoxic activity against a panel of human cancer cells (CC_{50} = 0.19-2.56 μ M) comparable to that of parent compound, but with especially high selectivity against certain human melanoma and breast cancers. *In vivo*, it exhibited superior activity to β -lapachone in the hollow fiber assay against a panel of 12 human tumor cell lines. Another related compound is:



304859: C21 H19 N O2

SOURCES – Universidad de Buenos Aires, Buenos Aires (AR); Universidad de Chile, Santiago de Chile (CL).

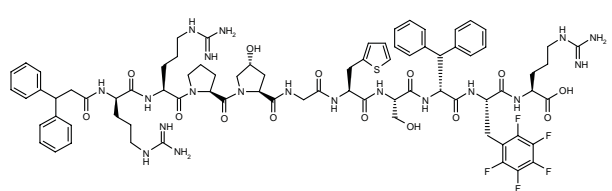
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1. Di Chenna, P.H. et al. *Preparation and cytotoxicity toward cancer cells of mono(arylimino) derivatives of β -lapachone.* J Med Chem 2001, 44(15): 2486.

B-10458

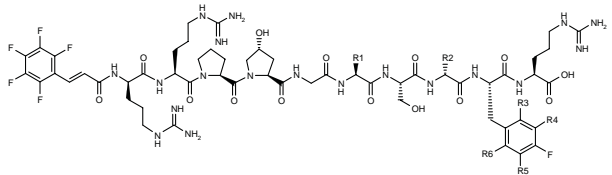
305457

N $^{\alpha}$ -(3,3-Diphenylpropionyl)-D-arginyl-L-arginyl-L-prolyl-(*trans*-4-hydroxy)-L-prolyl-glycyl-[3-(2-thienyl)]-L-alanyl-L-seryl-(3,3-diphenyl)-D-alanyl-(pentafluoro)-L-phenylalanyl-L-arginine



C79 H96 F5 N19 O14 S; Mol wt: 1662.8020

ACTION – Bradykinin (BK) antagonist with modest anti-BK activity but potent *in vitro* cytotoxic activity against small cell lung cancer cells (EC_{50} = 13 μ M). Potentially useful for the treatment of lung and prostate cancer. Other related compounds are:



Compound	R1	R2	R3=R4=R5=R6	Formula
B-10396 [305453]	2-indanyl	2-indanyl	H	C ₇₃ H ₉₁ F ₆ N ₁₉ O ₁₄
B-10410 [305455]	2-thienyl-CH2	CH(Ph)2	F	C ₇₃ H ₈₅ F ₁₀ N ₁₉ O ₁₄ S

SOURCE – University of Colorado, Boulder, CO (US).

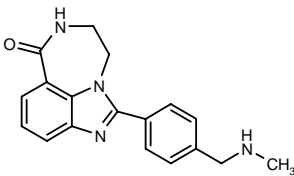
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

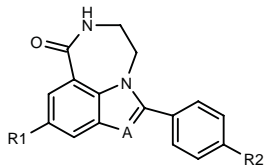
302331

2-[4-(Methylaminomethyl)phenyl]-4,5,6,7-tetrahydro-imidazo[4,5,1-jk][1,4]benzodiazepin-7-one



C18 H18 N4 O; Mol wt: 306.3672

ACTION – Poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor ($K_i = 1.9 \text{ nM}$) that exhibits a potentiation factor (IC_{50} topotecan or temozolomide alone/ IC_{50} topotecan or temozolomide in combination with test compound) of 1.8. Potentially useful as a potentiator of anticancer therapies and for inhibiting neurotoxicity following stroke, trauma and neuro-degenerative diseases. Other exemplified tricyclic compounds include the following:



Compound	R1	R2	A	Formula
302332	H	H	N	C ₁₆ H ₁₃ N ₃ O
302333	F	CH ₂ N(Me) ₂	N	C ₁₉ H ₁₉ FN ₄ O
302334	H	cyclopropyl-CH ₂ NHCH ₂	N	C ₂₁ H ₂₂ N ₄ O
302335	H	3-Pyr	N	C ₂₁ H ₁₆ N ₄ O
302336	H	2-pyrrolidiny	N	C ₂₀ H ₂₀ N ₄ O
302338	F	CH ₂ N(Me) ₂	CH	C ₂₀ H ₂₀ FN ₃ O
302340	H	1-pyrrolidiny-CH(Me)	N	C ₂₂ H ₂₄ N ₄ O

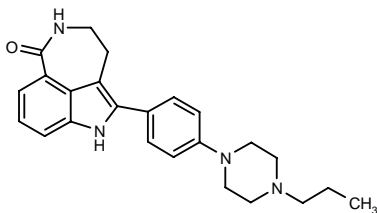
SOURCES – Agouron (Pfizer); Cancer Research Campaign.

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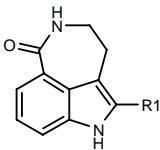
303329

2-[4-(4-Propylpiperazin-1-yl)phenyl]-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-6-one



C₂₄ H₂₈ N₄ O; Mol wt: 388.5122

ACTION – Inhibitor of PARP (poly[ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase), potentially useful for the treatment of neurological and neurodegenerative disorders, including cerebral ischemia, traumatic brain injury, stroke, Alzheimer’s disease, Huntington’s disease and epilepsy, as well as inflammatory disorders, diabetes and cancer. Other exemplified azepinoindole derivatives include the following:



Compound	R1	Formula
303330	4-(4-Bu-1-Piz)-Ph	C ₂₅ H ₃₀ N ₄ O
303331	4-(1-Piz-CH ₂ CH ₂ O)-Ph	C ₂₃ H ₂₆ N ₄ O ₂
303332	4-[4-(PhCH ₂)-1-Piz-CH ₂ CH ₂ O]-Ph	C ₃₀ H ₃₂ N ₄ O ₂
303333	4-(4-Bu-perhydro-1,4-diazepin-1-yl)-Ph	C ₂₆ H ₃₂ N ₄ O
303334	1-PhCH ₂ -4-Pip	C ₂₃ H ₂₆ N ₃ O
303335	1-i-Pr-4-Pip	C ₁₉ H ₂₅ N ₃ O

SOURCE – BASF.

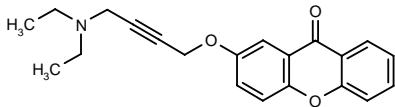
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VIB-100

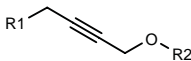
302494

2-[4-(Diethylamino)-2-butynyloxy]-9*H*-xanthen-9-one



C₂₁ H₂₁ N O₃; Mol wt: 335.4009

ACTION – Modulator of multidrug resistance (MDR), particularly MDR mediated by P-glycoprotein, proven to potently increase the cytotoxicity of paclitaxel against drug-resistant breast cancer MDA-435/LCC6-MDR cells when given at 1 μ M, IC_{50} values of paclitaxel in the absence and presence of this compound being 426 and 110 nM, respectively (70% reduction in IC_{50} value of paclitaxel); when tested alone, compound exhibited only low cytotoxicity against drug-resistant cancer cells ($IC_{50} > 30 \mu$ M). Other exemplified compounds from this series of flavone, xanthone and coumarin derivatives include the following:



Compound	R1	R2	Formula
VIB-16 [302495]	4-PhCH ₂ -1-Piz	3-(4-MeO-Ph)-4-oxo-4 <i>H</i> -1-benzopyran-7-yl	C ₃₁ H ₃₀ N ₂ O ₄
VIB-94 [302497]	N(Et) ₂	4-Me-2-oxo-2 <i>H</i> -1-benzopyran-7-yl	C ₁₈ H ₂₁ NO ₃
VIB-99 [302499]	4-morpholinyl	9-oxo-9 <i>H</i> -xanthen-1-yl	C ₂₁ H ₁₉ NO ₄

SOURCE – Indena.

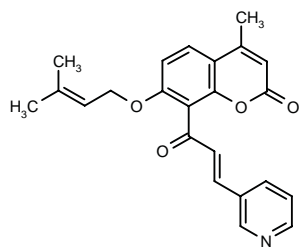
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VIB-106

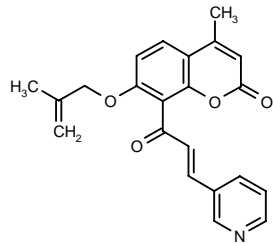
302501

4-Methyl-7-(3-methyl-2-butenyloxy)-8-[3-(3-pyridyl)-2-propenoyl]-2*H*-1-benzopyran-2-one



C23 H21 N O4; Mol wt: 375.4219

ACTION – Modulator of multidrug resistance (MDR), particularly MDR mediated by P-glycoprotein, proven to potently increase the cytotoxicity of paclitaxel against drug-resistant breast cancer MDA-435/LCC6-MDR cells when given at 1 μ M, IC₅₀ values of paclitaxel in the absence and presence of this compound being 426 and 130 nM, respectively (70% reduction in IC₅₀ value of paclitaxel); when tested alone, compound exhibited only low cytotoxicity against drug-resistant cancer cells (IC₅₀ > 1 μ M). Another exemplified compound from this series of chalcone derivatives is:



VIB-122 [302510]: C22 H19 N O4

SOURCE – Indena.

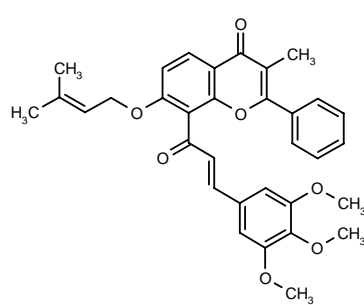
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VIB-173

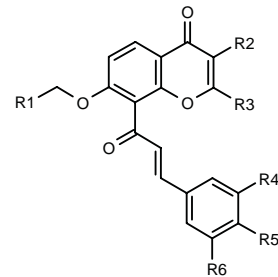
302511

3-Methyl-7-(3-methyl-2-butenyloxy)-2-phenyl-8-[3-(3,4,5-trimethoxyphenyl)-2-propenoyl]-4*H*-1-benzopyran-4-one



C33 H32 O7; Mol wt: 540.6088

ACTION – Modulator of multidrug resistance (MDR), particularly MDR mediated by P-glycoprotein, proven to potently increase the cytotoxicity of paclitaxel against drug-resistant breast cancer MDA-435/LCC6-MDR cells when given at 1 μ M, IC₅₀ values of paclitaxel in the absence and presence of this compound being 426 and 21 nM, respectively (95% reduction in IC₅₀ value of paclitaxel); when tested alone, compound exhibited only low cytotoxicity against drug-resistant cancer cells (IC₅₀ > 1 μ M). Other exemplified compounds from this series of chalcone derivatives include the following:



Compound	R1	R2	R3	R4=R5=R6	Formula
VIB-167 [302512]	ethynyl	Me	Ph	H	C ₂₈ H ₂₀ O ₄
VIB-178 [302513]	CH=C(Me)2	-CH=CHCH=CH-		OMe	C ₃₀ H ₂₈ O ₇

SOURCE – Indena.

REFERENCES

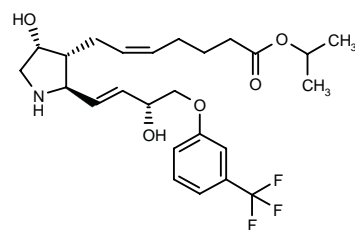
1. Bombardelli, E. and Valenti, P. (Indena SpA) *Novel chalcones*. WO 0117988.

OCULAR MEDICATIONS

302370

7-[4(*R*)-Hydroxy-2(*R*)-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]pyrrolidin-3(*R*)-yl]-5(*Z*)-heptenoic acid isopropyl ester

11-Deoxy-16-[3-(trifluoromethyl)phenoxy]-11-aza-17,18,19,20-tetranorprostaglandin F_{2α} isopropyl ester



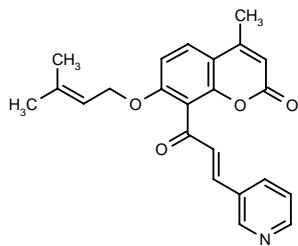
C25 H34 F3 N O5; Mol wt: 485.5396

ACTION – Agent for the treatment of glaucoma and ocular hypertension, reported to exhibit an improved therapeutic profile over prostaglandin F_{2α} (PGF_{2α}). Other specifically claimed compounds from this series of 11-aza analogues of PGF_{2α} are:

VIB-106

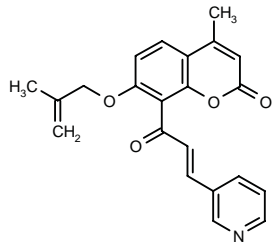
302501

4-Methyl-7-(3-methyl-2-butenyloxy)-8-[3-(3-pyridyl)-2-propenoyl]-2*H*-1-benzopyran-2-one



C23 H21 N O4; Mol wt: 375.4219

ACTION – Modulator of multidrug resistance (MDR), particularly MDR mediated by P-glycoprotein, proven to potently increase the cytotoxicity of paclitaxel against drug-resistant breast cancer MDA-435/LCC6-MDR cells when given at 1 μ M, IC₅₀ values of paclitaxel in the absence and presence of this compound being 426 and 130 nM, respectively (70% reduction in IC₅₀ value of paclitaxel); when tested alone, compound exhibited only low cytotoxicity against drug-resistant cancer cells (IC₅₀ > 1 μ M). Another exemplified compound from this series of chalcone derivatives is:



VIB-122 [302510]: C22 H19 N O4

SOURCE – Indena.

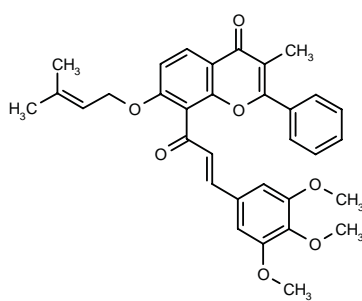
REFERENCES

1. Bombardelli, E. and Valenti, P. (Indena SpA) *Chalcone coumarins*. WO 0117984.

VIB-173

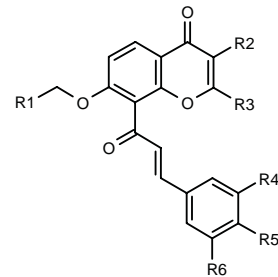
302511

3-Methyl-7-(3-methyl-2-butenyloxy)-2-phenyl-8-[3-(3,4,5-trimethoxyphenyl)-2-propenoyl]-4*H*-1-benzopyran-4-one



C33 H32 O7; Mol wt: 540.6088

ACTION – Modulator of multidrug resistance (MDR), particularly MDR mediated by P-glycoprotein, proven to potently increase the cytotoxicity of paclitaxel against drug-resistant breast cancer MDA-435/LCC6-MDR cells when given at 1 μ M, IC₅₀ values of paclitaxel in the absence and presence of this compound being 426 and 21 nM, respectively (95% reduction in IC₅₀ value of paclitaxel); when tested alone, compound exhibited only low cytotoxicity against drug-resistant cancer cells (IC₅₀ > 1 μ M). Other exemplified compounds from this series of chalcone derivatives include the following:



Compound	R1	R2	R3	R4=R5=R6	Formula
VIB-167 [302512]	ethynyl	Me	Ph	H	C ₂₈ H ₂₀ O ₄
VIB-178 [302513]	CH=C(Me)2	-CH=CHCH=CH-		OMe	C ₃₀ H ₂₈ O ₇

SOURCE – Indena.

REFERENCES

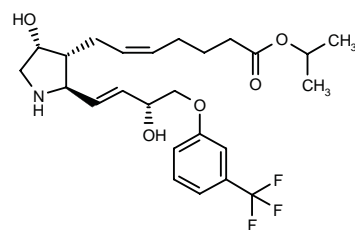
1. Bombardelli, E. and Valenti, P. (Indena SpA) *Novel chalcones*. WO 0117988.

OCULAR MEDICATIONS

302370

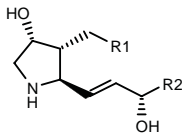
7-[4(*R*)-Hydroxy-2(*R*)-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]pyrrolidin-3(*R*)-yl]-5(*Z*)-heptenoic acid isopropyl ester

11-Deoxy-16-[3-(trifluoromethyl)phenoxy]-11-aza-17,18,19,20-tetranorprostaglandin F_{2α} isopropyl ester



C25 H34 F3 N O5; Mol wt: 485.5396

ACTION – Agent for the treatment of glaucoma and ocular hypertension, reported to exhibit an improved therapeutic profile over prostaglandin F_{2α} (PGF_{2α}). Other specifically claimed compounds from this series of 11-aza analogues of PGF_{2α} are:



Compound	R1	R2	Formula
302371	(Z)-i-PrOCO(CH2)3CH=CH	2-indanyl	C ₂₆ H ₃₇ NO ₄
302372	(Z)-i-PrOCOCH2CH2CH=CHCH2	3-Cl-PhOCH2	C ₂₄ H ₃₄ ClNO ₅

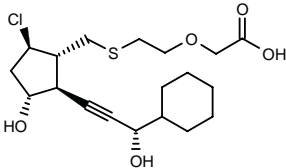
SOURCE – Alcon.

REFERENCES

1. Hellberg, M.R. and Klimko, P.G. (Alcon Laboratories, Inc.) *11-Aza prostaglandins for the treatment of glaucoma and ocular hypertension*. US 6211226.

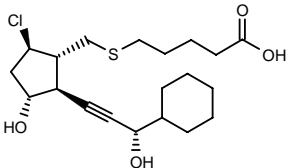
303143

9-Chloro-15-cyclohexyl-9-deoxy-13,14-didehydro-16,17,18,19,20-pentanor-3-oxa-6-thiaprostaglandin F_{1β}



C19 H29 Cl O5 S; Mol wt: 404.9521

ACTION – Agent with excellent prostaglandin D₂ (PGD₂)-like agonist activity, proven to stimulate cAMP production in bovine fetal trachea-derived EBTr [NBL-4] cells (EC₅₀ = 5.13 nM vs. EC₅₀ = 124 nM for PGD₂). Potentially useful for inducing sleep, as well as for the treatment of nephropathy, ischemic cardiopathy, ciculatory diseases such as heart failure and hypertension, and glaucoma. Another compound from this series of prostaglandin derivatives is:



303145: C20 H31 Cl O4 S

SOURCE – Taisho.

REFERENCES

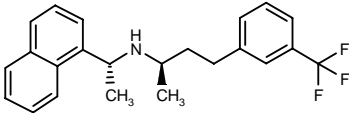
1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin derivs*. WO 0119790.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

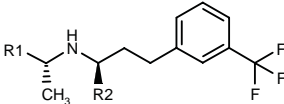
302359

N-[1(R)-Methyl-3-[3-(trifluoromethyl)phenyl]propyl]-N-[1(R)-(1-naphthyl)ethyl]amine



C23 H24 F3 N; Mol wt: 371.4436

ACTION – Agent with the ability to modulate inorganic ion receptors and particularly cell-surface calcium receptors, giving an EC₅₀ value of 0.019 μM for increasing intracellular Ca²⁺ in Fura-2-loaded parathyroid cells. Potentially useful for inhibiting bone resorption, for decreasing parathyroid hormone levels and in the treatment of hyperparathyroidism, Paget’s disease, hypercalcemia, osteoporosis, hypertension and renal osteodystrophy. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
302361	3-MeO-Ph	Me	C ₂₀ H ₂₄ F ₃ NO
302362	1-Naph	H	C ₂₂ H ₂₂ F ₃ N

SOURCE – NPS Pharmaceuticals.

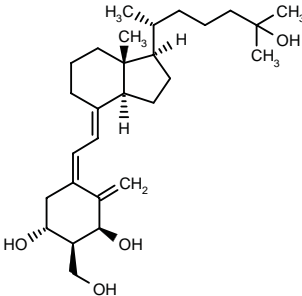
REFERENCES

1. Van Wagenen, B.C. et al. (NPS Pharmaceuticals, Inc.) *Calcium receptor-active cpds*. US 6211244.

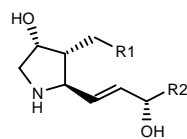
302947

(1*S*,2*S*,3*R*,5*Z*,7*E*)-2-(Hydroxymethyl)-9,10-secocholesta-5,7,10-triene-1,3,25-triol

1α,25-Dihydroxy-2α-(hydroxymethyl)vitamin D₃



C28 H46 O4; Mol wt: 446.6674



Compound	R1	R2	Formula
302371	(Z)-i-PrOCO(CH2)3CH=CH	2-indanyl	C ₂₆ H ₃₇ NO ₄
302372	(Z)-i-PrOCOCH2CH2CH=CHCH2	3-Cl-PhOCH2	C ₂₄ H ₃₄ ClNO ₅

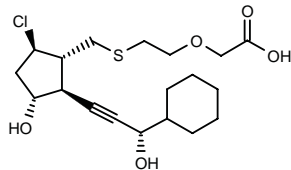
SOURCE – Alcon.

REFERENCES

1. Hellberg, M.R. and Klimko, P.G. (Alcon Laboratories, Inc.) *11-Aza prostaglandins for the treatment of glaucoma and ocular hypertension*. US 6211226.

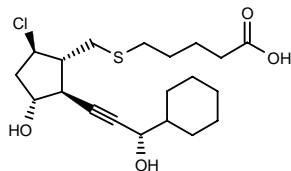
303143

9-Chloro-15-cyclohexyl-9-deoxy-13,14-didehydro-16,17,18,19,20-pentanor-3-oxa-6-thiaprostaglandin F_{1β}



C19 H29 Cl O5 S; Mol wt: 404.9521

ACTION – Agent with excellent prostaglandin D₂ (PGD₂)-like agonist activity, proven to stimulate cAMP production in bovine fetal trachea-derived EBTr [NBL-4] cells (EC₅₀ = 5.13 nM vs. EC₅₀ = 124 nM for PGD₂). Potentially useful for inducing sleep, as well as for the treatment of nephropathy, ischemic cardiopathy, ciculatory diseases such as heart failure and hypertension, and glaucoma. Another compound from this series of prostaglandin derivatives is:



303145: C20 H31 Cl O4 S

SOURCE – Taisho.

REFERENCES

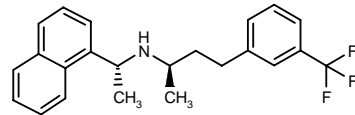
1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin derivs*. WO 0119790.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

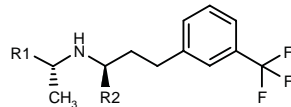
302359

N-[1(R)-Methyl-3-[3-(trifluoromethyl)phenyl]propyl]-N-[1(R)-(1-naphthyl)ethyl]amine



C23 H24 F3 N; Mol wt: 371.4436

ACTION – Agent with the ability to modulate inorganic ion receptors and particularly cell-surface calcium receptors, giving an EC₅₀ value of 0.019 μM for increasing intracellular Ca²⁺ in Fura-2-loaded parathyroid cells. Potentially useful for inhibiting bone resorption, for decreasing parathyroid hormone levels and in the treatment of hyperparathyroidism, Paget’s disease, hypercalcemia, osteoporosis, hypertension and renal osteodystrophy. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
302361	3-MeO-Ph	Me	C ₂₀ H ₂₄ F ₃ NO
302362	1-Naph	H	C ₂₂ H ₂₂ F ₃ N

SOURCE – NPS Pharmaceuticals.

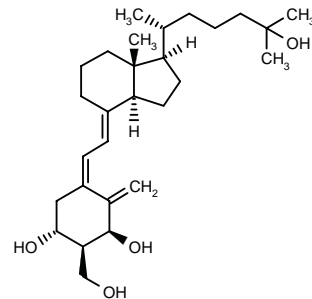
REFERENCES

1. Van Wagenen, B.C. et al. (NPS Pharmaceuticals, Inc.) *Calcium receptor-active cpds*. US 6211244.

302947

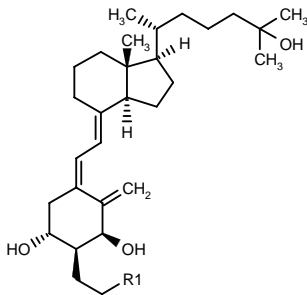
(1*S*,2*S*,3*R*,5*Z*,7*E*)-2-(Hydroxymethyl)-9,10-secocholesta-5,7,10-triene-1,3,25-triol

1α,25-Dihydroxy-2α-(hydroxymethyl)vitamin D₃



C28 H46 O4; Mol wt: 446.6674

ACTION – Vitamin D₃ derivative with affinity for vitamin D receptors (VDR), potentially useful for the treatment of calcium metabolism disorders and cancer, as well as for use as an immunomodulating agent. Other compounds from this series of vitamin D₃ derivatives having substituents at the 2α-position include the following:



Compound	R1	Formula
302948	OH	C ₂₉ H ₄₈ O ₄
302949	H	C ₂₉ H ₄₈ O ₃
302950	Me	C ₃₀ H ₅₀ O ₃

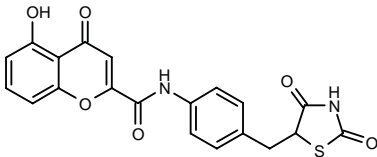
SOURCE – Chugai.

REFERENCES

1. Takayama, H. et al. (Chugai Pharmaceutical Co. Ltd.) *Vitamin D derivs. having substituents at the 2α-position*. WO 0116099.

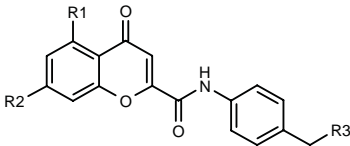
302951

N-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenyl]-5-hydroxy-4-oxo-4*H*-1-benzopyran-2-carboxamide



C20 H14 N2 O6 S; Mol wt: 410.4046

ACTION – Agent for the treatment of bone diseases with osteogenesis-promoting activity, as demonstrated in rat femoral bone marrow cells by a significant increase in alkaline phosphatase activity at a concentration of 10 μM. Other exemplified compounds from this series of chromone derivatives include the following:



Compound	R1=R2	R3	Formula
302952	H	2,4-dioxo-5-oxazolidinyl	C ₂₀ H ₁₄ N ₂ O ₆
302953	H	4-morpholinyl	C ₂₁ H ₂₀ N ₂ O ₄
302954	H	2,4-dioxo-5-thiazolidinyl	C ₂₀ H ₁₄ N ₂ O ₅ S
302955	OH	2,4-dioxo-5-thiazolidinyl	C ₂₀ H ₁₄ N ₂ O ₇ S

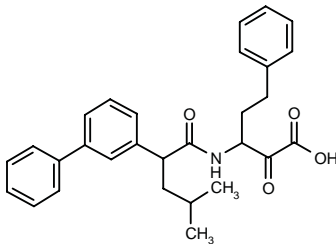
SOURCE – Takeda.

REFERENCES

1. Yasuma, T. et al. (Takeda Chemical Industries, Ltd.) *Chromone derivs., process for the preparation of the same and uses thereof*. JP 2001139571, WO 0116127.

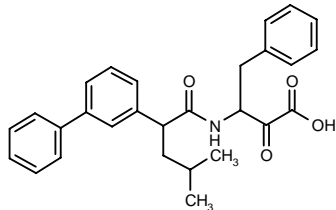
302972

3-[2-(Biphenyl-3-yl)-4-methylpentanamido]-2-oxo-5-phenylpentanoic acid

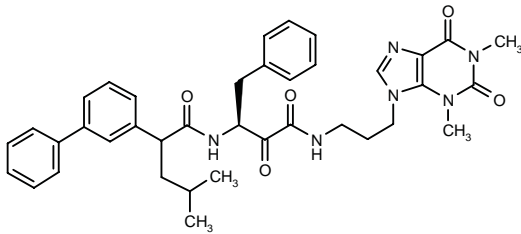


C29 H31 N O4; Mol wt: 457.5669

ACTION – An inhibitor of cysteine proteases such as cathepsin L (IC₅₀ = 90 nM), cathepsin B (IC₅₀ = 365 nM), cathepsin S (IC₅₀ = 29 nM) and papain (IC₅₀ = 13 nM), with potential for the treatment of osteoporosis, rheumatoid arthritis and Alzheimer's disease, as well as Behçet's disease, asthma, thrombosis, cerebral ischemia, apoptosis, cancer metastasis, cataracts and neuronal death, and as an immunosuppressant. Other exemplified compounds from this series of biaryl acetic acid amide derivatives include the following:



302973: C28 H29 N O4



302974: C38 H42 N6 O5

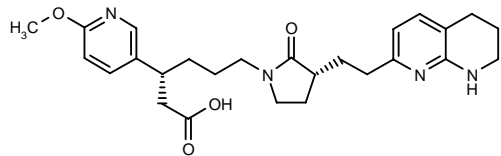
SOURCE – Kissei.

REFERENCES

1. Sato, M. et al. (Kissei Pharmaceutical Co., Ltd.) *Biaryl acetic acid amide derivs.* JP 2001055366.

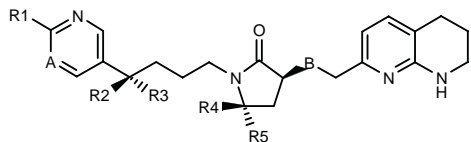
303443

3(*R*)-(6-Methoxypyridin-3-yl)-6-[2-oxo-3(*R*)-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl]-hexanoic acid

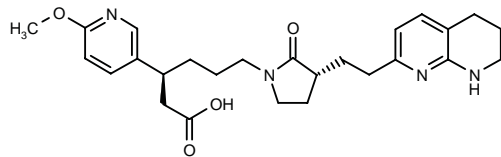


C26 H34 N4 O4; Mol wt: 466.5786

ACTION – Integrin, particularly $\alpha_v\beta_3$ (vitronectin receptor) and/or $\alpha_v\beta_5$, antagonist useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	A	B	Formula
303445	OMe	CH2CO2H	H	H	H	CH	CH2	C ₂₆ H ₃₄ N ₄ O ₄
303446	OMe	H	CH2CO2H	H	H	CH	CH2	C ₂₆ H ₃₄ N ₄ O ₄
303449	OMe	CH2CO2H	H	H	Me	CH	CH2	C ₂₇ H ₃₆ N ₄ O ₄
303451	OMe	CH2CO2H	H	Me	H	CH	CH2	C ₂₇ H ₃₆ N ₄ O ₄
303452	OMe	CH2CO2H	H	Me	H	CH	NH	C ₂₆ H ₃₅ N ₅ O ₄
303453	Me	CH2CO2H	H	Me	H	N	NH	C ₂₅ H ₃₄ N ₆ O ₃
303454	OMe	CH2CO2H	H	H	H	N	CH2	C ₂₅ H ₃₃ N ₅ O ₄
303455	OMe	H	CH2CO2H	Me	H	N	CH2	C ₂₆ H ₃₅ N ₅ O ₄
303457	OMe	H	CH2CO2H	H	Me	N	CH2	C ₂₆ H ₃₅ N ₅ O ₄



303444: C26 H34 N4 O4

SOURCE – Merck & Co.

REFERENCES

1. Askew, B.C. and Smith, G.R. (Merck & Co., Inc.) *Integrin receptor antagonists*. WO 0124797.

305368

L-Alanyl-L-valyl-L-alanyl-L-glutamyl-L-isoleucyl-L-glutaminy-L-leucyl-L-methionyl-L-histidyl-L-glutaminy-L-homoarginyl-L-alanyl-L-lysyl-L-tryptophan

C76 H123 N23 O19 S; Mol wt: 1695.0160

ACTION – Potent analogue of the synthetic parathyroid hormone PTH(1-14), with an EC₅₀ value of 60 nM for cAMP formation. Potentially useful for the treatment of metabolic bone diseases such as osteoporosis.

SOURCES – Harvard Medical School, Boston, MA (US); Massachusetts General Hospital, Boston, MA (US).

REFERENCES

1. Khatri, A. et al. *Minimization of parathyroid hormone using simultaneous multiple peptide synthesis: Implications for strcuture-based drug design*. 17th Am Peptide Symp (June 9-14, San Diego) 2001, Abst P532.

305435

[Glu^{22,25},Leu^{23,28,31},Aib²⁹,Lys^{26,30}]hPTHrP(1-34)NH₂

L-Alanyl-L-valyl-L-seryl-L-glutamyl-L-histidyl-L-glutaminy-L-leucyl-L-leucyl-L-histidyl-L-aspartyl-L-lysyl-glycyl-L-lysyl-L-seryl-L-isoleucyl-L-glutaminy-L-aspartyl-L-leucyl-L-arginyl-L-arginyl-L-arginyl-L-glutamyl-L-leucyl-L-leucyl-L-glutamyl-L-lysyl-L-leucyl-L-leucyl-2-aminoisobutyryl-L-lysyl-L-leucyl-L-histidyl-L-threonyl-L-alaninamide

C174 H300 N56 O49; Mol wt: 3960.6270

ACTION – Human parathyroid hormone (hPTH)-related protein that is significantly more potent than native hPTH(1-34)NH₂ in stimulating bone growth in animals. Considered a promising candidate for the development of a bone anabolic agent for the treatment of osteoporosis.

SOURCE – Biomeasure.

REFERENCES

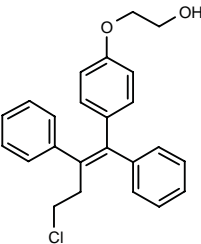
1. Dong, Z.X. (Biomeasure Inc.) *Analogs of parathyroid hormone*. JP 2001508439, WO 9830590.
2. Dong, J.Z. et al. *Highly potent analogs of human parathyroid hormone and human parathyroid hormone-related protein*. 17th Am Peptide Symp (June 9-14, San Diego) 2001, Abst P414.

OSPEMIFENE

289319

2-[4-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy]-ethanol

FC-1271a



C24 H23 Cl O2; Mol wt: 378.8967

ACTION – Selective estrogen receptor modulator (SERM), a metabolite of toremifene found in patients on toremifene therapy that specifically binds to estrogen ER α and ER β receptors with affinity similar to tamoxifen and toremifene. In osteoporotic ovariectomized rats, compound (1-10 mg/kg p.o.) prevented the ovariectomy-induced bone loss and increase in serum cholesterol levels, with no significant effect on uterine wet weight or morphology. Compound showed a strong antitumor effect against mammary carcinoma induced by DMBA in mice, whereas it had very little effect on the estrogen-dependent proliferation of human breast cancer MCF-7 and ZR 75-1 cell lines *in vitro* and *in vivo*. In healthy postmenopausal women, 12-week treatment with compound at 60 or 90 mg was associated with bone turnover comparable to that obtained with raloxifene. An increase in serum gonadotropin levels was seen during treatment, whereas no changes were seen in serum levels of LDL or HDL cholesterol. Compound did not induce endometrial stimulation but, in contrast to raloxifene, it exerted an estrogenic effect on vaginal and ectocervical cells and it was shown to relieve menopausal symptoms. Potentially useful particularly for the treatment of postmenopausal osteoporosis.

SOURCES – Hormos; Orion Corporation.

REFERENCES

1. Degregorio, M. et al. (Orion Corporation) *Triphenylethylenes for the prevention and treatment of osteoporosis*. WO 9607402.

2. Härkönen, P. et al. (Orion Corporation) *Serum cholesterol lowering agent*. WO 9732574.

3. Anttila, M. et al. *Pharmacokinetics of toremifene*. J Steroid Biochem 1990, 36(3): 249-52.

4. Berthou, F. and Dreano, Y. *High-performance liquid chromatographic analysis of tamoxifen, toremifene and their major human metabolites*. J Chromatogr - Biomed Appl 1993, 616(1): 117.

5. Berthou, F. et al. *Involvement of cytochrome P450 3A enzyme family in the major metabolic pathways of toremifene in human liver microsomes*. Biochem Pharmacol 1994, 47(10): 1883.

6. Cunningham, A. et al. *A study of the structural basis of the carcinogenicity of tamoxifen, toremifene and their metabolites*. Mutat Res 1996, 349(1): 85.

7. De Gregorio, M.W. et al. *Pharmacokinetics of (deaminohydroxy)toremifene in humans: A new, selective estrogen-receptor modulator*. Eur J Clin Pharmacol 2000, 56(6-7): 469.

8. Erkkola, R.U. et al. *Comparison of FC1271a, a novel SERM, and raloxifene in postmenopausal women: A 12-week clinical phase II study*. Bone 2001, 28(5, Suppl.): Abst P601 W.

9. Hasan, S.A. et al. *Quantitative analysis of toremifene metabolites in biological specimens by high-performance liquid chromatography*. Anal Lett 1990, 23(2): 327.

10. Hellmann Blumberg, U. et al. *Genotoxic effects of the novel mixed antiestrogen FC-1271a in comparison to tamoxifen and toremifene*. Breast Cancer Res Treat 2000, 60(1): 63.

11. Kangas, L. *Biochemical and pharmacological effects of toremifene metabolites*. Cancer Chemother Pharmacol 1990, 27(1): 8-12.

12. Kapyla, H. et al. *High-dose toremifene in advanced renal-cell carcinoma*. Cancer Chemother Pharmacol 1997, 39(6): 547.

13. Lim, C.K. et al. *High performance liquid chromatography of toremifene and metabolites*. J Liq Chromatogr 1994, 17(8): 1773.

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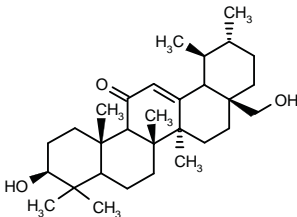
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TREATMENT OF LIPOPROTEIN DISORDERS

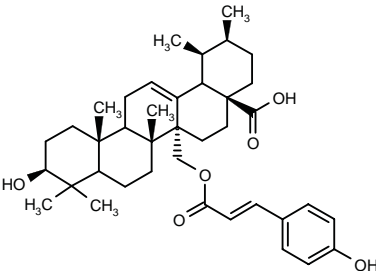
302109

3 β ,28-Dihydroxyurs-12-en-11-one



C30 H48 O3; Mol wt: 456.7062

ACTION – An inhibitor of ACAT shown to produce 41 and 79% inhibition of enzyme from rat hepatic microsomes at 0.05 and 0.2 mg/ml, respectively. Potentially useful for the treatment of arteriosclerosis. Another exemplified compound from this series of triterpene derivatives is:



302110: C39 H54 O6

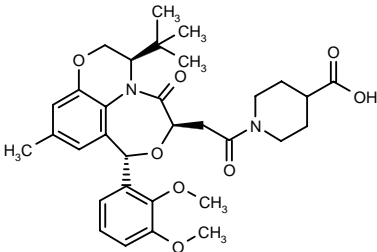
SOURCE – Pola Chemical.

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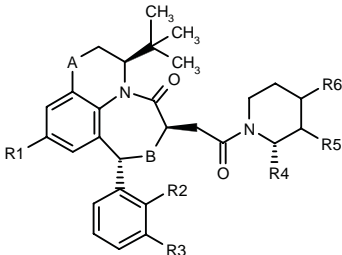
302186

1-[2-[3(*R*)-*tert*-Butyl-8(*S*)-(2,3-dimethoxyphenyl)-10-methyl-5-oxo-2,3,5,6-tetrahydro-8*H*-[1,4]oxazino[2,3,4-*jk*]-[4,1]benzoxazepin-6(*R*)-yl]acetyl]piperidine-4-carboxylic acid



C32 H40 N2 O8; Mol wt: 580.6740

ACTION – Squalene synthase inhibitor with potential for the treatment of hypercholesterolemia, hypertriglyceridemia, atherosclerosis, fungal infections, Alzheimer's disease and acne. Other specifically claimed tricyclic compounds are:



Compound	R1	R2	R3	R4	R5	R6	A	B	Formula
302187	Me	OMe	OMe	H	(<i>R</i>)-CO2H	H	CH2	O	C ₃₃ H ₄₂ N ₂ O ₇
302189	Me	OMe	OMe	H	CO2H	H	CH2	O	C ₃₃ H ₄₂ N ₂ O ₇
302190	Me	OMe	OMe	CO2H	H	H	CH2	O	C ₃₃ H ₄₂ N ₂ O ₇
302191	Cl	-O(CH2)2O-		H	H	CO2H	CH2	O	C ₃₂ H ₃₇ ClN ₂ O ₇
302192	Cl	-O(CH2)2O-		H	CO2H	H	CH2	O	C ₃₂ H ₃₇ ClN ₂ O ₇
302193	Cl	-O(CH2)2O-		H	(<i>R</i>)-CO2H	H	CH2	O	C ₃₂ H ₃₇ ClN ₂ O ₇
302194	Cl	-OCH2O-		H	H	CO2H	CH2	O	C ₃₁ H ₃₅ ClN ₂ O ₇
302195	Cl	OMe	OMe	H	H	CO2H	O	O	C ₃₁ H ₃₇ ClN ₂ O ₈
302196	Cl	OMe	H	H	H	CO2H	O	O	C ₃₀ H ₃₅ ClN ₂ O ₇
302197	Me	OMe	H	H	H	CO2H	O	O	C ₃₁ H ₃₈ N ₂ O ₇
302198	Me	OMe	OMe	H	H	CO2H	O	S	C ₃₂ H ₄₀ N ₂ O ₇ S
302199	Cl	OMe	H	H	H	CO2H	CH2	S	C ₃₁ H ₃₇ ClN ₂ O ₆ S
302200	Me	OMe	H	H	H	CO2H	CH2	O	C ₃₂ H ₄₀ N ₂ O ₆

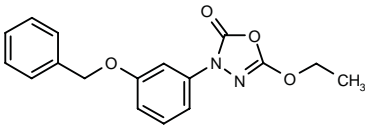
SOURCE – Pfizer.

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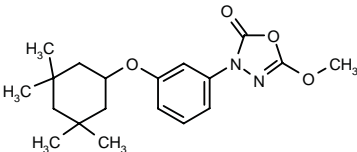
302463

3-[3-(Benzyloxy)phenyl]-5-ethoxy-1,3,4-oxadiazol-2(3*H*)-one



C17 H16 N2 O4; Mol wt: 312.3234

ACTION – Agent for the treatment of hyperlipidemia, hyperglycemia, non-insulin-dependent diabetes mellitus, diabetic syndrome and pancreatic damage, a hormone-sensitive lipase (HSL) inhibitor (IC₅₀ < 1 μM against partially purified rat enzyme). Another exemplified compound from this series of substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones is:



302464: C19 H26 N2 O4

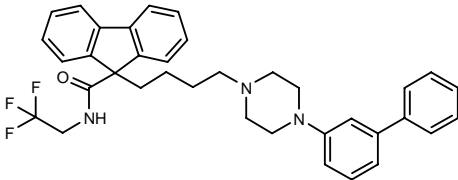
SOURCE – Aventis Pharma.

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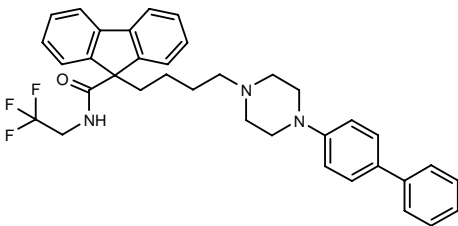
303150

9-[4-[4-(Biphenyl-3-yl)piperazin-1-yl]butyl]-*N*-(2,2,2-trifluoroethyl)-9*H*-fluorene-9-carboxamide



C36 H36 F3 N3 O; Mol wt: 583.6944

ACTION – Microsomal triglyceride transfer protein (MTP) inhibitor that may be useful for the treatment of hyperlipidemia, atherosclerosis, diabetes mellitus, obesity and pancreatitis. Another specifically claimed substituted piperazine derivative is:



303151: C36 H36 F3 N3 O

SOURCE – Boehringer Ingelheim.

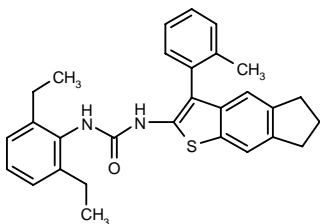
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R-755*

215871

N-(2,6-Diethylphenyl)-*N'*-[3-(2-methylphenyl)-6,7-dihydro-5*H*-indeno[5,6-*b*]thiophen-2-yl]urea



C29 H30 N2 O S; Mol wt: 454.6390

ACTION – Potent hypolipidemic agent, an ACAT inhibitor with IC₅₀ values of 2.5-64 nM for ACAT in rabbit intestinal microsomes and several cell lines including human colon adenocarcinoma Caco-2, human monocytic leukemia THP-1 and murine monocyte-macrophage J774A.1 cells. In cholesterol-fed rats and hamsters, compound in the diet reduced serum cholesterol levels (ED₅₀ = 0.84 and 1.74 mg/kg, respectively) and liver total cholesterol (ED₅₀ = 0.24 and < 0.3 mg/kg, respectively). In cholesterol-fed rabbits, compound at doses of 0.1 and 1 mg/kg reduced total plasma cholesterol (50.6 and 85.2%, respectively), plasma triglycerides (73.0 and 76.5%, respectively) and liver total cholesterol content (77.8% at 1 mg/kg). In this model, compound also significantly reduced ACAT activities in the aortic arch and thoracic aorta. In cholesterol-fed rabbits with established atherosclerosis, it dose-dependently (0.1-10 mg/kg) reduced the surface area of atherosclerotic involvement and cholesterol contents in the aorta.

SOURCE – Nihon Nohyaku.

REFERENCES

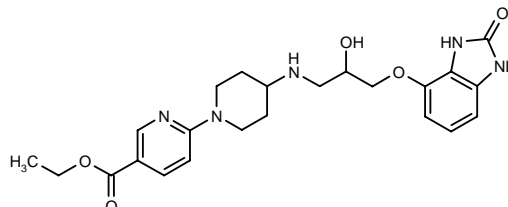
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*Identified compound **215871** (see **214660**) Drug Data Rep 1995, 017(01): 0100.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

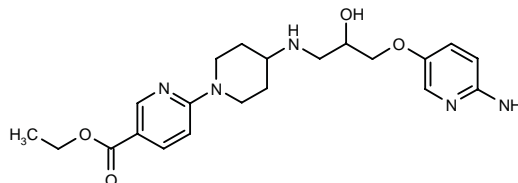
302364

6-[4-[2-Hydroxy-3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yloxy)propylamino]piperidin-1-yl]pyridine-3-carboxylic acid ethyl ester



C23 H29 N5 O5; Mol wt: 455.5121

ACTION – Selective β_3 -adrenoceptor agonist with low toxicity, potentially useful for the treatment of gastro-intestinal disorders such as irritable bowel syndrome, as an intestinal motility modulator, as a lipolytic, antiobesity, antidiabetic, psychotropic and antidepressant, as well as for the treatment or prevention of glaucoma, dysmenorrhea and for preventing preterm labor. Another specifically claimed compound from this series of heteroaryloxy propanolamines is:



302365: C21 H29 N5 O4

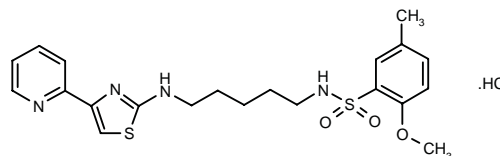
SOURCE – Sanofi-Synthélabo.

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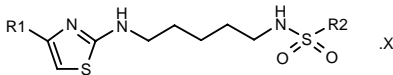
302388

2-Methoxy-5-methyl-*N*-[5-[4-(2-pyridyl)thiazol-2-ylamino]pentyl]benzenesulfonamide hydrochloride



C21 H26 N4 O3 S2 . HCl; Mol wt: 483.0543

ACTION – Selective neuropeptide Y (NPY) Y₅ receptor antagonist, as demonstrated by a K_i value of 2.7 nM in a binding assay using cloned human Y₅ receptors, compared to K_i values of > 10,000 nM for human Y₁, Y₂ and Y₄ receptors. Functional antagonism was demonstrated in the forskolin-stimulated cAMP assay in cells stably transfected with the cloned human Y₅ receptor (pK_b = 7.8). Potentially useful for the treatment of eating disorders (obesity and bulimia), sexual/reproductive disorders, depression, epileptic seizures, hypertension, cerebral hemorrhage, congestive heart failure and sleep disorders. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	X	Formula
302390	4-Pyr	2-MeO-5-Me-Ph	HCl	C ₂₁ H ₂₆ N ₄ O ₃ S ₂ .HCl
302392	3-thienyl	N(Me)2		C ₁₄ H ₂₂ N ₄ O ₂ S ₃

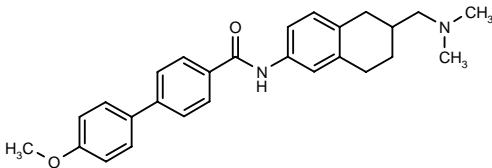
SOURCE – Synaptic.

REFERENCES

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303163

N-[6-(Dimethylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]-4'-methoxybiphenyl-4-carboxamide



C27 H30 N2 O2; Mol wt: 414.5460

ACTION – Agent for the treatment or prevention of obesity, a melanin-concentrating hormone (MCH) antagonist, as demonstrated *in vitro* in a GTP-γS binding assay using the human MCH receptor (known as SLC-1) cloned in CHO cells (IC₅₀ = 40 nM). A representative compound from a series of cyclic and acyclic amine derivatives.

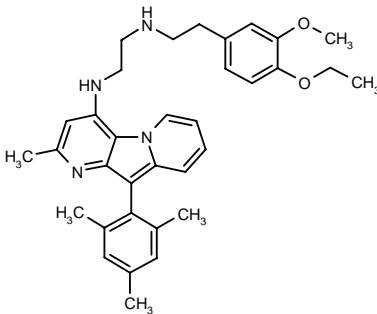
SOURCE – Takeda.

REFERENCES

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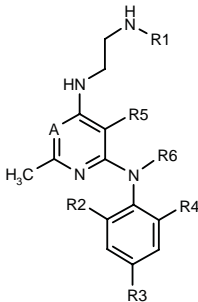
303294

*N*¹-[2-(4-Ethoxy-3-methoxyphenyl)ethyl]-*N*²-[2-methyl-10-(2,4,6-trimethylphenyl)pyrido[2,3-*b*]indolizin-4-yl]ethane-1,2-diamine

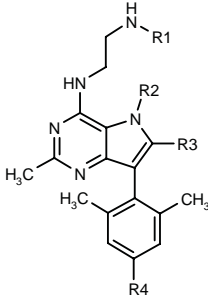


C34 H40 N4 O2; Mol wt: 536.7160

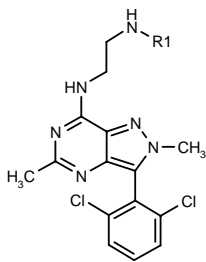
ACTION – Agent for the treatment of disorders characterized by excess neuropeptide Y (NPY) such as eating disorders including obesity and bulimia, and certain cardiovascular diseases including hypertension and congestive heart failure, a selective NPY Y₁ receptor antagonist. Other exemplified compounds within this series of alkylene diamine-substituted heterocycles include the following:



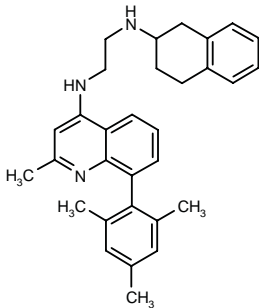
Compound	R1	R2	R3	R4	R5	R6	A	Formula
303361	3-MeO-4-EtO-Ph-CH2CH2	Me	Me	Me	-C(Me)=C(Me)-	N		C ₃₁ H ₄₁ N ₅ O ₂
303363	3-MeO-4-EtO-Ph-CH2CH2	Me	Me	Me	-N=CH-	CH		C ₂₉ H ₃₇ N ₅ O ₂
303364	cyclohexyl	Me	Me	Me	-N=C(Me)-	CH		C ₂₅ H ₃₅ N ₅
303365	cyclopentyl	H	Cl	Cl	-N=C(Me)-	CH		C ₂₁ H ₂₅ Cl ₂ N ₅
303369	3-MeO-4-EtO-Ph-CH2CH2	Me	Me	Me	-N=N-	CH		C ₂₈ H ₃₆ N ₆ O ₂
303370	cyclopentyl	Me	Me	Me	-N=N-	CH		C ₂₂ H ₃₀ N ₆
303371	cyclohexyl	H	i-Pr	Br	-NHCO-	N		C ₂₃ H ₃₁ BrN ₆ O
303374	3-MeO-4-EtO-Ph-CH2CH2	Me	Me	Me	H	H	N	C ₂₇ H ₃₇ N ₅ O ₂



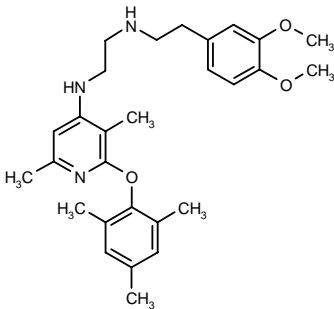
Compound	R1	R2	R3	R4	Formula
303360	cyclopentyl	-CH=CHCH=CH-	Me		C ₂₇ H ₃₃ N ₅
303362	4-MeO-PhCH2CH2	Me	H	OMe	C ₂₈ H ₃₅ N ₅ O ₂



Compound	R1	Formula
303366	cyclopentyl	C ₂₀ H ₂₄ Cl ₂ N ₆
303367	3-MeO-4-EtO-PhCH2CH2	C ₂₆ H ₃₀ Cl ₂ N ₆ O ₂



303372: C31 H35 N3



303373: C28 H37 N3 O3

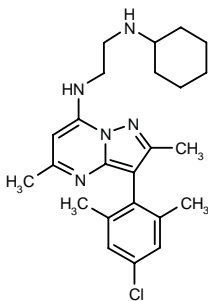
SOURCES – Neurogen; Pfizer.

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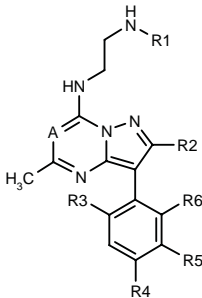
303295

N¹-[3-(4-Chloro-2,6-dimethylphenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-yl]-N²-cyclohexylethane-1,2-diamine



C24 H32 Cl N5; Mol wt: 426.0048

ACTION – Agent for the treatment of disorders characterized by excess neuropeptide Y (NPY) such as eating disorders including obesity and bulimia, and certain cardiovascular diseases including hypertension and congestive heart failure, a selective NPY Y₁ receptor antagonist. Other exemplified compounds within this series of amino-substituted pyrazolo[1,5-a]pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines include the following:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
303296	cyclopentyl	Me	H	OMe	H	OMe	CH	C ₂₃ H ₃₁ N ₅ O ₂
303297	cyclopentyl	Me	Me	OMe	H	Me	CH	C ₂₄ H ₃₃ N ₅ O
303298	cyclopentyl	CF3	H	Cl	H	Cl	CH	C ₂₁ H ₂₂ Cl ₂ F ₃ N ₅
303299	cyclopentyl	Me	Me	OMe	H	Me	N	C ₂₃ H ₃₂ N ₆ O
303300	cyclopentyl	Me	Cl	OEt	H	Cl	N	C ₂₂ H ₂₈ Cl ₂ N ₆ O
303301	cyclohexyl	Me	H	F	H	Cl	CH	C ₂₂ H ₂₇ ClFN ₅
303302	cyclopentyl	Me	H	F	H	Cl	CH	C ₂₁ H ₂₅ ClFN ₅
303303	cyclopentyl	Me	H	OEt	H	Cl	CH	C ₂₃ H ₃₀ ClN ₅ O
303304	cyclopentyl	Me	Cl	H	H	F	CH	C ₂₁ H ₂₅ ClFN ₅
303305	cyclopentyl	Me	H	H	H	Cl	CH	C ₂₁ H ₂₆ ClN ₅
303306	cyclopentyl	Me	H	Br	H	F	CH	C ₂₁ H ₂₅ BrFN ₅
303307	cyclopentyl	Me	H	H	H	F	CH	C ₂₁ H ₂₆ FN ₅
303308	cyclopentyl	Me	H	H	Cl	Cl	CH	C ₂₁ H ₂₅ Cl ₂ N ₅

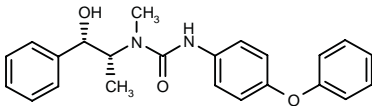
SOURCES – Neurogen; Pfizer.

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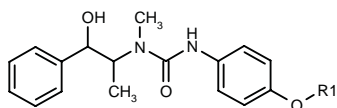
305649

N-[2(S)-Hydroxy-1(R)-methyl-2-phenylethyl]-N-methyl-N'-(4-phenoxyphenyl)urea



C23 H24 N2 O3; Mol wt: 376.4536

ACTION – Neuropeptide Y₅ receptor antagonist with high selectivity for human Y₅ receptors (IC₅₀ = 6.5 nM) over human Y₁ and Y₂ receptors (IC₅₀ > 10,000 nM) and *in vitro* functional antagonist activity (K_i = 24 nM). Potentially useful for the treatment of obesity. Other related compounds are:



Compound	R1	Isomer	Formula
305650	CH ₂ Ph	1R,2S	C ₂₄ H ₂₆ N ₂ O ₃
305651	Ph	1S,2R	C ₂₃ H ₂₄ N ₂ O ₃

SOURCE – Amgen.

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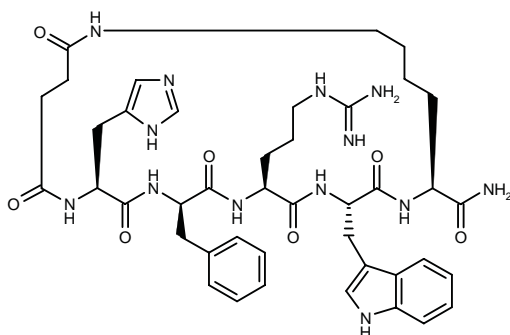
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MJK-1

305447

N-Succinyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-L-lysineamide *N*-6.5-*C*-4,1-lactam



C42 H55 N13 O7; Mol wt: 853.9805

ACTION – α -Melanocyte-stimulating hormone (α -MSH) agonist analogue with high selectivity for the human melanocortin receptor MC₄ (IC₅₀ = 6.6 nM); compound showed agonist activity for the human MC₄ receptor similar to the nonselective agonist MTII (EC₅₀ = 6.1 and 5 nM, respectively). Potentially useful for the treatment of eating and energy homeostasis disorders.

SOURCE – University of Arizona, Tucson, AZ (US).

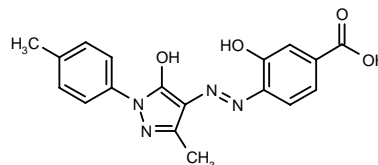
REFERENCES

1. Kavarana, M.J. et al. *The design and evaluation of a novel selective and potent agonist of human melanocortin receptor 4*. 17th Am Peptide Symp (June 9-14, San Diego) 2001, Abst P424.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

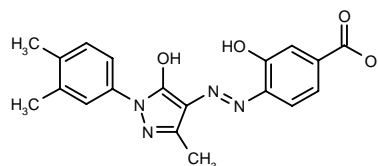
302567

3-Hydroxy-4-[5-hydroxy-3-methyl-1-(4-methylphenyl)-1*H*-pyrazol-4-yl]diazenyl]benzoic acid



C18 H16 N4 O4; Mol wt: 352.3484

ACTION – Nonpeptide thrombopoietin (TPO) mimetic that promotes thrombopoiesis and megakaryocytopoiesis and is potentially useful for the treatment of thrombocytopenia and other conditions associated with depressed platelet production. Another exemplified compound is:



302568: C19 H18 N4 O4

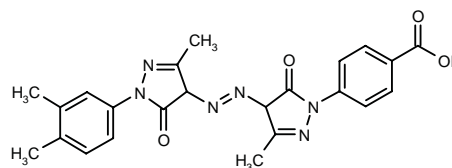
SOURCE – GlaxoSmithKline.

REFERENCES

1. Luengo, J.I. and Duffy, K.J. (SmithKline Beecham Corp.) *Thrombopoietin mimetics*. WO 0117349.

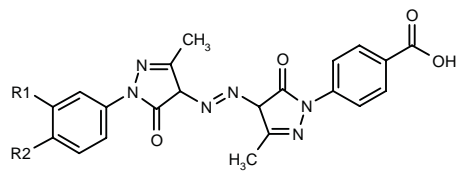
303038

4-[4-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl]diazenyl]-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]benzoic acid



C23 H22 N6 O4; Mol wt: 446.4648

ACTION – Thrombopoietin (TPO) mimetic that promotes thrombopoiesis and megakaryocytopoiesis. This compound produced 56% of the maximal TPO effect, with an EC₅₀ of 0.72 μ M in a luciferase assay in TPO-responsive murine BaF3 cells, and is expected to be useful for the treatment of thrombocytopenia and other conditions with depressed platelet production. Other exemplified compounds are:



Compound	R1	R2	Formula
303039	CF3	H	C ₂₂ H ₁₇ F ₃ N ₆ O ₄
303040	H	I	C ₂₁ H ₁₇ IN ₆ O ₄

SOURCE – GlaxoSmithKline.

REFERENCES

1. Duffy, K.J. et al. (SmithKline Beecham Corp.) *Thrombopoietin mimetics*. WO 0121180.

DARBEPOETIN ALFA

USAN

236400

Hyperglycosylated protein analogue of recombinant human erythropoietin (rhuEPO) produced by recombinant DNA technology in CHO cells. It is designed by substituting five amino acids in the primary sequence of rhuEPO to create two extra consensus N-linked glycosylation sites (Asn-X-Ser/Thr), resulting in five N-linked carbohydrate chains, a molecular weight of 38,000 Da and a carbohydrate content of 52%

[30-L-Asparagine,32-L-threonine,87-L-valine,88-L-asparagine,90-L-threonine]erythropoietin(human)

Novel erythropoiesis-stimulating protein
NESP⁺

ACTION – Erythropoiesis-stimulating protein produced using recombinant techniques in CHO cells.

INDICATION – Treatment of anemia in chronic kidney failure including patients on and not yet on dialysis.

PRESENTATION – Prefilled syringe containing solution for injection, 10 µg/0.4 ml (25 µg/ml).

PROPRIETARY NAME – ARANESP (DE, GB).

SOURCE – Amgen.

REFERENCES

1. Akahori, H. et al. *The effect of novel erythropoiesis stimulating protein (NESP) on anemia in a rat model of cisplatin-induced renal failure*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 847.

2. Akahori, H. et al. *The effect of novel erythropoiesis stimulating protein (NESP) on anemia induced by renal failure in rats*. Exp Hematol 1998, 26(8): 766.

3. Cooke, K. et al. *Anemia of chronic disease (ACD) in a rodent model is similar to human ACD and can be alleviated by ARANESP treatment*. Annu Eur Congr Rheumatol (June 13-16, Prague) 2001, Abst THU0040.

4. Cooke, K. et al. *Novel erythropoiesis stimulating protein (NESP) alleviates anemia associated with chronic inflammatory disease in a rodent model*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 209.

5. Egrie, J.C. et al. *Novel erythropoiesis stimulating protein (NESP) has a longer serum half-life and greater in vivo biological activity than recombinant human erythropoietin (rHuEPO)*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 243.

6. Elliott, S.G. et al. *Rational design of novel erythropoiesis stimulating protein (Aranesp™): A super-sialated molecule with increased biological activity*. Blood 2000, 96(11, Part 1): Abst 352.

7. Glaspy, J. et al. *Novel erythropoiesis stimulating protein (NESP) exhibits a prolonged serum half life (t1/2) in oncology patients (pts)*. Proc Am Soc Clin Oncol 2000, 19: Abst 210.

8. Glaspy, J. et al. *Randomised, active-controlled phase I/II dose escalation study of novel erythropoiesis stimulating protein (NESP) in patients with solid tumours (presented by the NESP Oncology Study Group)*. Ann Oncol 2000, 11(Suppl. 4): Abst 667O.

9. Glaspy, J. et al. *Randomized, active-controlled, phase I/II, dose-escalation study of Aranesp™ in solid tumor patients*. Blood 2000, 96(11, Part 1): Abst 1278.

10. Glaspy, J.A. et al. *Randomized, active-controlled, phase 1/2, dose-escalation study of NESP administered weekly and every 2 weeks in patients with solid tumors*. Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1546.

11. Hartley, C. et al. *Pre-treatment with novel erythropoiesis stimulating protein (NESP) prevents chemotherapy induced anemia in mice*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 213.

12. Heatherington, A. et al. *Predictability of pharmacokinetic properties of NESP administered once every 3 weeks in patients with nonmyeloid malignancies receiving cyclic chemotherapy*. Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 471.

13. Heatherington, A.C. et al. *Establishment of a PK-PD relationship for novel erythropoiesis stimulating protein (NESP) in dogs*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

14. Hedenus, M. et al. *A randomized, blinded, placebo-controlled, phase II, dose-finding study of novel erythropoiesis stimulating protein (NESP) in patients with lymphoproliferative malignancies*. Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1569.

15. Macdougall, I.C. *Novel erythropoiesis stimulating protein (NESP) for the treatment of renal anemia*. J Am Soc Nephrol 1998, 9: Abst A1317.

16. Macdougall, I.C. et al. *Comparison of the pharmacokinetics of novel erythropoiesis stimulating protein (NESP) and epoetin alfa (rhEPO) in dialysis patients*. J Am Soc Nephrol 1997, 8: Abst A1233.

17. Macdougall, I.C. et al. *Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients*. J Am Soc Nephrol 1999, 10(11): 2392.

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19. Smith, R.E. et al. *Open-label, phase I/II dose escalation study of NESP in patients with chronic anemia of cancer*. Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1574.

20. Vanreterghem, Y. et al. *Novel erythropoiesis stimulating protein (NESP) maintains hemoglobin (Hgb) in ESRD patients when administered once weekly or once every other week*. 32nd Annu Meet Am Soc Nephrol (ASN) (Nov 5-8, Miami Beach) 1999, Abst A1365.

21. *Amgen and Genesis Pharma sign distribution agreement for ARANESP*. DailyDrugNews.com (Daily Essentials) 2001, Jan 23.

23. *Amgen announces 31 percent increase in earnings per share*. Amgen Inc. Press Release 1996, April 17.

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26. *Amgen highlights Q4 and full-year 2000 developments*. DailyDrugNews.com (Daily Essentials) 2001, Jan 29.

27. *Amgen launches ARANESP in the E.U.* DailyDrugNews.com (Daily Essentials) 2001, June 26.

28. *Amgen reviews third quarter developments*. DailyDrugNews.com (Daily Essentials) 2000, Nov 17.

29. *Amgen's ARANESP recommended for approval by CPMP*. DailyDrugNews.com (Daily Essentials) 2001, March 20.

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34. *Four Amgen products under regulatory review.* DailyDrugNews.com (Daily Essentials) 2001, May 9.

35. *Kirin accelerates development of NESP in Asia.* DailyDrugNews.com (Daily Essentials) 2001, Feb 26.

36. *Kirin Beer starting clinical R&D in South East Asia: First of all TPO and then 3 new products in Taiwan.* Kagaku Kogyo Nippo 1996, September 25.

37. *Longer acting treatment for anemia in chronic renal failure cleared for U.S. launch.* DailyDrugNews.com (Daily Essentials) 2001, Sept 20.

38. *Pipeline update included in Amgen's second quarter report.* DailyDrugNews.com (Daily Essentials) 2001, July 31.

39. *sBLA submitted for ARANESP.* DailyDrugNews.com (Daily Essentials) 2001, Sept 25.

40. *USAN Council. List No. 432.* Clin Pharmacol Ther 2000, 68(5): 581.

MONOGRAPH – Cases, A. *Novel Erythropoiesis Stimulating Protein.* Drugs Fut 2000, 25(3): 0246.

*Drug Data Rep 2000, 022(05): 0477.

TREATMENT OF DISORDERS OF
PURINE AND PYRIMIDINE
METABOLISM

RASBURICASE

Prop INN

229807

Recombinant urate oxidase

SR-29142

ACTION – Recombinant urate oxidase with potent uricolytic activity.

INDICATION – Treatment and prophylaxis of acute hyperuricemia to prevent acute renal failure in patients with hematological malignancy with a high tumor burden and at risk of rapid tumor lysis or shrinkage at initiation of chemotherapy.

PRESENTATION – Powder, 1.5 mg and solvent for concentrate for solution for infusion.

PROPRIETARY NAME – Fasturtec (GB).

SOURCE – Sanofi-Synthelabo.

REFERENCES

1. Dussossoy, D. et al. *Development of a two-site immunoassay of recombinant urate oxidase (SR 29142) and its use for determination of pharmacokinetic parameters in rats and baboons.* J Pharm Sci 1996, 85(9): 955.

2. Goldman, S. et al. *Recombinant urate oxidase (SR29142) lowers uric acid faster and more effectively than allopurinol in children with high risk leukemia or lymphoma (LOL) and tumor lysis syndrome (TLS): Results of an open-label, randomized trial.* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2801.

3. Goldman, S.C. et al. *A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis.* Blood 2001, 97(10): 2998.

4. Jacob, F. et al. *New drug to lower uric acid levels in healthy volunteers. Advances on prevention and control of hyperuricemia in malignancies?* Proc Amer Assoc Cancer Res 1996, 37: Abst 1464.

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8. Schaison, G. et al. *Administration of recombinant urate oxidase SR29142 for prevention of hyperuricemia in 54 patients with acute leukemias (AL) or non-Hodgkin lymphomas (NHL).* Proc Amer Assoc Cancer Res 1997, 38: Abst 1501.

9. *Another major European launch for enzyme therapy for use in tumor lysis syndrome.* DailyDrugNews.com (Daily Essentials) 2001, Oct 1.

10. *European approval granted for Sanofi-Synthelabo's Fasturtec.* DailyDrugNews.com (Daily Essentials) 2001, March 30.

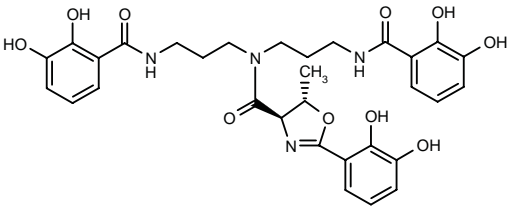
11. *Recombinant urate oxidase now available for acute tumor lysis syndrome.* DailyDrugNews.com (Daily Essentials) 2001, June 19.

TREATMENT OF POISONING, DRUG
ABUSE AND DEPENDENCY

D-FLUVIABACTIN²

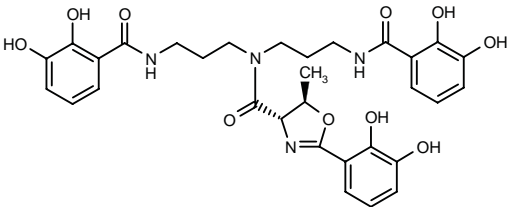
305443

N,N-Bis[3-(2,3-dihydroxybenzamido)propyl]-2-(2,3-dihydroxyphenyl)-5(*S*)-methyl-4,5-dihydrooxazole-4(*R*)-carboxamide



C31 H34 N4 O10; Mol wt: 622.6276

ACTION – Synthetic iron chelator, the unnatural enantiomer of **L-fluviabactin**, a microbial iron chelator isolated from *Vibrio fluvialis*. D-Fluviabactin was very effective at clearing iron from bile duct-cannulated rats, with an efficiency similar to L-fluviabactin. However, the unnatural enantiomer did not promote bacterial growth like other siderophores, and it may therefore be suitable as a therapeutic iron chelator for the treatment of iron overload syndromes secondary to chronic transfusion therapy such as aplastic anemia and thalassemia.



L-Fluviabactin [305442]:¹⁻³ C31 H34 N4 O10

SOURCE – University of Florida, Gainesville, FL (US).

REFERENCES

1. Bergeron, R.J. Jr. (University of Florida) *Synthesis of parabactin and homologs thereof.* US 4565874.

2. Bergeron, R.J. et al. *Significance of asymmetric sites in choosing siderophores as deferration agents.* J Med Chem 2001, 44(15): 2469.

3. Yamamoto, S. et al. *Structures of two polyamine-containing catecholate siderophores from Vibrio fluvialis.* J Biochem (Tokyo) 1993, 113(5): 538.

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6. Pui, C.-H. and Jeha, S. *Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia: The compassionate use experience.* Blood 2000, 96(11, Part 1): Abst 3106.

7. Pui, C.-H. et al. *Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma.* J Clin Oncol 2001, 19(3): 697.

8. Schaison, G. et al. *Administration of recombinant urate oxidase SR29142 for prevention of hyperuricemia in 54 patients with acute leukemias (AL) or non-Hodgkin lymphomas (NHL).* Proc Amer Assoc Cancer Res 1997, 38: Abst 1501.

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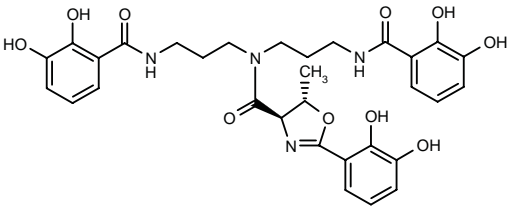
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TREATMENT OF POISONING, DRUG
ABUSE AND DEPENDENCY

D-FLUVIABACTIN²

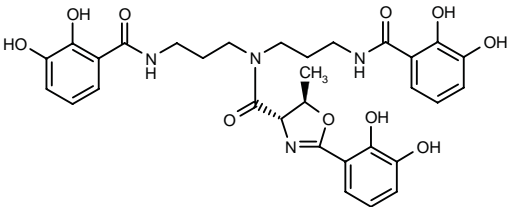
305443

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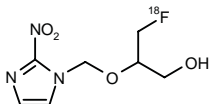
2. Bergeron, R.J. et al. *Significance of asymmetric sites in choosing siderophores as deferration agents.* J Med Chem 2001, 44(15): 2469.

3. Yamamoto, S. et al. *Structures of two polyamine-containing catecholate siderophores from Vibrio fluvialis.* J Biochem (Tokyo) 1993, 113(5): 538.

DIAGNOSTIC AGENTS

302679

3-[¹⁸F]Fluoro-2-(2-nitro-1*H*-imidazol-1-ylmethoxy)propan-1-ol



C7 H10 F N3 O4; Mol wt: 218.1730

ACTION – A representative compound from a series of nitroimidazole derivatives useful as diagnostic imaging agents for the ischemic sites of circulatory organs and cancer cells. Effective imaging of rat ischemic heart was observed following i.v. administration. In addition, compound was shown to selectively distribute into tumors compared to blood or other organs following i.v. administration to mice bearing squamous cell carcinoma or fibrosarcoma.

SOURCE – Pola Chemical.

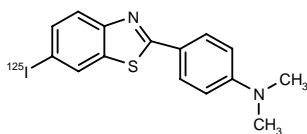
REFERENCES

1. Takai, Y. et al. (Pola Chemical Industries Inc.) *Nitroimidazole deriv. and diagnostic imaging agent containing the same*. WO 0119799.

TZDM

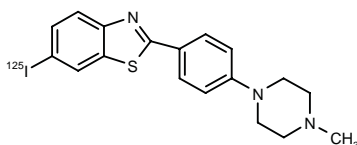
304492

N-[4-(6-[¹²⁵I]iodobenzothiazol-2-yl)phenyl]-*N,N*-dimethylamine



C15 H13 I N2 S; Mol wt: 378.3477

ACTION – Selective ligand for β -amyloid peptide (A β) aggregates (K_d = 0.06 and 0.14 nM for A β [1-40] and A β [1-42] aggregates, respectively). Biodistribution studies using the radioiodinated compound showed excellent brain uptake and retention (maximum uptake at 60 min of 1.57% dose/organ). Moreover, radioiodinated compound resulted in excellent autoradiographic visualization of amyloid plaques in postmortem brain sections of a patient with Down's syndrome, which contain primarily A β (1-42) aggregates. Potentially useful as a biomarker for detecting A β aggregates in Alzheimer's disease brains. Another related compound is:



TZPI [304493]: C18 H18 I N3 S

SOURCE – University of Pennsylvania, Philadelphia, PA (US).

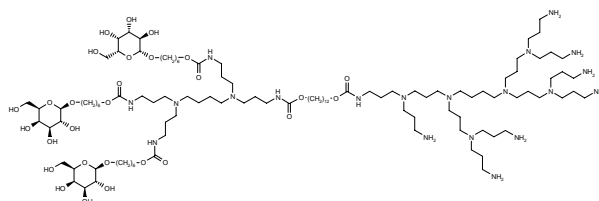
REFERENCES

1. Zhuang, Z.-P. et al. *Radioiodinated styrylbenzenes and thioflavins as probes for amyloid aggregates*. J Med Chem 2001, 44(12): 1905.

DRUG DELIVERY

302438

Dodecane-1,12-diol mixed ester with *N*-[4-(3-amino-propyl)-8,13,13-tris[3-[*N,N*-bis(3-aminopropyl)amino]-propyl]-4,8,13-triazatridecyl]carbamate and *N*-[4,9,9-tris[3-[6-(β -D-galactopyranosyloxy)hexyloxy-carboxamido]propyl]-4,9-diazanonyl]carbamate



C109 H224 N20 O28; Mol wt: 2263.0810

ACTION – Bifunctional cationic compound, a targetable DNA vector shown to efficiently deliver a gene into HepG2 cells in preliminary *in vitro* transfection experiments. Potentially useful for delivering genes into targeted cells *in vivo*.

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

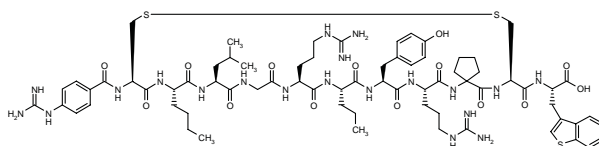
REFERENCES

1. Ren, T. et al. *Synthesis of bifunctional cationic compound for gene delivery*. Tetrahedron Lett 2001, 42(6): 1007.

PHARMACOLOGICAL TOOLS

304110

N-[1-[*N*-(4-Guanidinobenzoyl)-L-cysteinyl-L-norleucyl-L-leucyl-glycyl-L-arginyl-L-norvalyl-L-tyrosyl-L-arginyl-amino]cyclopentylcarbonyl]-L-cysteinyl-3-(benzothien-3-yl)-L-alanine cyclic (1-9)-disulfide

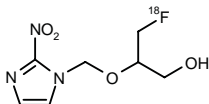


C71 H102 N20 O14 S3; Mol wt: 1555.9110

DIAGNOSTIC AGENTS

302679

3-[¹⁸F]Fluoro-2-(2-nitro-1*H*-imidazol-1-ylmethoxy)propan-1-ol



C7 H10 F N3 O4; Mol wt: 218.1730

ACTION – A representative compound from a series of nitroimidazole derivatives useful as diagnostic imaging agents for the ischemic sites of circulatory organs and cancer cells. Effective imaging of rat ischemic heart was observed following i.v. administration. In addition, compound was shown to selectively distribute into tumors compared to blood or other organs following i.v. administration to mice bearing squamous cell carcinoma or fibrosarcoma.

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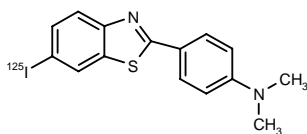
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TZDM

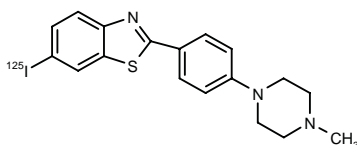
304492

N-[4-(6-[¹²⁵I]iodobenzothiazol-2-yl)phenyl]-*N,N*-dimethylamine



C15 H13 I N2 S; Mol wt: 378.3477

ACTION – Selective ligand for β -amyloid peptide (A β) aggregates (K_d = 0.06 and 0.14 nM for A β [1-40] and A β [1-42] aggregates, respectively). Biodistribution studies using the radioiodinated compound showed excellent brain uptake and retention (maximum uptake at 60 min of 1.57% dose/organ). Moreover, radioiodinated compound resulted in excellent autoradiographic visualization of amyloid plaques in postmortem brain sections of a patient with Down's syndrome, which contain primarily A β (1-42) aggregates. Potentially useful as a biomarker for detecting A β aggregates in Alzheimer's disease brains. Another related compound is:



TZPI [304493]: C18 H18 I N3 S

SOURCE – University of Pennsylvania, Philadelphia, PA (US).

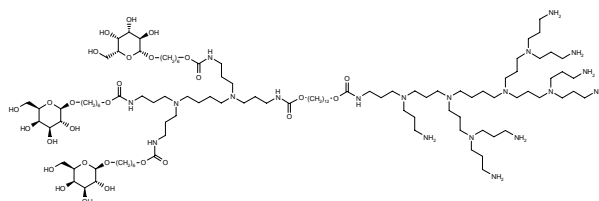
REFERENCES

1. Zhuang, Z.-P. et al. *Radioiodinated styrylbenzenes and thioflavins as probes for amyloid aggregates*. J Med Chem 2001, 44(12): 1905.

DRUG DELIVERY

302438

Dodecane-1,12-diol mixed ester with *N*-[4-(3-amino-propyl)-8,13,13-tris[3-[*N,N*-bis(3-aminopropyl)amino]-propyl]-4,8,13-triazatridecyl]carbamate and *N*-[4,9,9-tris[3-[6-(β -D-galactopyranosyloxy)hexyloxy-carboxamido]propyl]-4,9-diazanonyl]carbamate



C109 H224 N20 O28; Mol wt: 2263.0810

ACTION – Bifunctional cationic compound, a targetable DNA vector shown to efficiently deliver a gene into HepG2 cells in preliminary *in vitro* transfection experiments. Potentially useful for delivering genes into targeted cells *in vivo*.

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

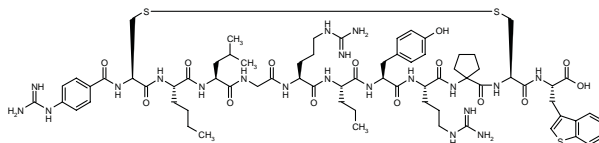
REFERENCES

1. Ren, T. et al. *Synthesis of bifunctional cationic compound for gene delivery*. Tetrahedron Lett 2001, 42(6): 1007.

PHARMACOLOGICAL TOOLS

304110

N-[1-[*N*-(4-Guanidinobenzoyl)-L-cysteinyl-L-norleucyl-L-leucyl-glycyl-L-arginyl-L-norvalyl-L-tyrosyl-L-arginyl-amino]cyclopentylcarbonyl]-L-cysteinyl-3-(benzothien-3-yl)-L-alanine cyclic (1-9)-disulfide

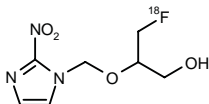


C71 H102 N20 O14 S3; Mol wt: 1555.9110

DIAGNOSTIC AGENTS

302679

3-[¹⁸F]Fluoro-2-(2-nitro-1*H*-imidazol-1-ylmethoxy)propan-1-ol



C7 H10 F N3 O4; Mol wt: 218.1730

ACTION – A representative compound from a series of nitroimidazole derivatives useful as diagnostic imaging agents for the ischemic sites of circulatory organs and cancer cells. Effective imaging of rat ischemic heart was observed following i.v. administration. In addition, compound was shown to selectively distribute into tumors compared to blood or other organs following i.v. administration to mice bearing squamous cell carcinoma or fibrosarcoma.

SOURCE – Pola Chemical.

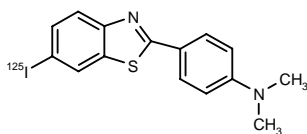
REFERENCES

1. Takai, Y. et al. (Pola Chemical Industries Inc.) *Nitroimidazole deriv. and diagnostic imaging agent containing the same*. WO 0119799.

TZDM

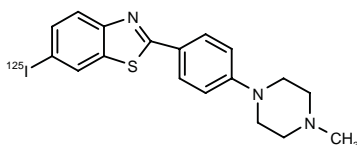
304492

N-[4-(6-[¹²⁵I]iodobenzothiazol-2-yl)phenyl]-*N,N*-dimethylamine



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TZPI [304493]: C18 H18 I N3 S

SOURCE – University of Pennsylvania, Philadelphia, PA (US).

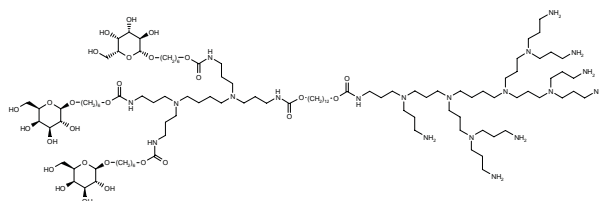
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DRUG DELIVERY

302438

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C109 H224 N20 O28; Mol wt: 2263.0810

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SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

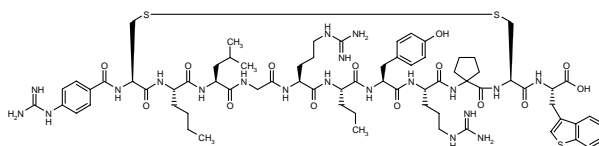
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PHARMACOLOGICAL TOOLS

304110

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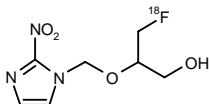


C71 H102 N20 O14 S3; Mol wt: 1555.9110

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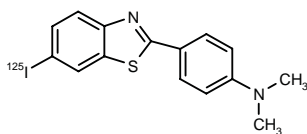
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TZDM

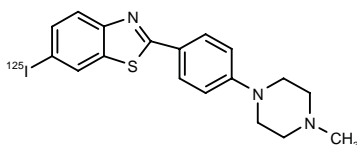
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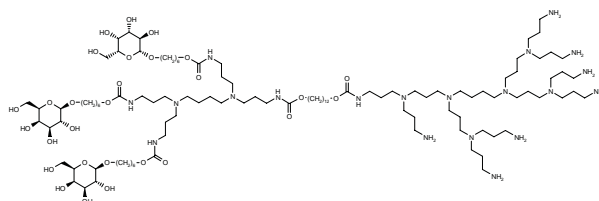
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DRUG DELIVERY

302438

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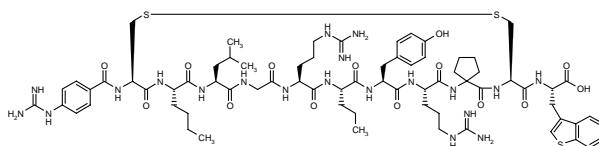
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1. Ren, T. et al. *Synthesis of bifunctional cationic compound for gene delivery*. Tetrahedron Lett 2001, 42(6): 1007.

PHARMACOLOGICAL TOOLS

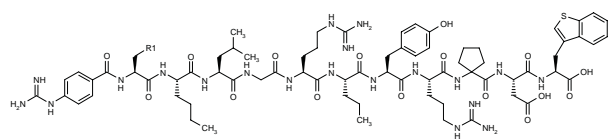
304110

N-[1-[*N*-(4-Guanidinobenzoyl)-L-cysteinyl-L-norleucyl-L-leucyl-glycyl-L-arginyl-L-norvalyl-L-tyrosyl-L-arginyl-amino]cyclopentylcarbonyl]-L-cysteinyl-3-(benzothien-3-yl)-L-alanine cyclic (1-9)-disulfide



C71 H102 N20 O14 S3; Mol wt: 1555.9110

ACTION – Stable melanin-concentrating hormone (MCH) receptor SLC-1 antagonist ($K_B = 148$ nM), potentially useful as a tool for the design of new MCH receptor radioligands for both *in vitro* and *in vivo* characterization of MCH functions. Other related compounds are:



Compound	R1	Formula
304119	CH2NH2	C ₇₃ H ₁₀₇ N ₂₁ O ₁₆ S
304124	NH2	C ₇₂ H ₁₀₅ N ₂₁ O ₁₆ S

SOURCES – CNRS; Servier.

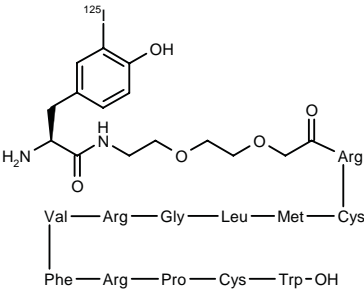
REFERENCES

1. Audinot, V. et al. *Structure-activity relationship studies of melanin-concentrating hormone (MCH)-related peptide ligands at SLC-1, the human MCH receptor*. J Biol Chem 2001, 276(17): 13554.

[¹²⁵I]-S-36057

305117

*N*α-[2-[2-[2-(3-[¹²⁵I]Iodo-L-tyrosylamino)ethoxy]-ethoxy]acetyl]-L-arginyl-L-cysteinyl-L-methionyl-L-leucyl-glycyl-L-arginyl-L-valyl-L-phenylalanyl-L-arginyl-L-prolyl-L-cysteiny-L-tryptophan



C82 H125 I N24 O18 S3; Mol wt: 1956.2380

ACTION – Potent radioligand for the melanin-concentrating hormone (MCH) receptor able to selectively label MHC receptors expressed in both HEK293 and CHO cells ($K_d = 0.037$ and 0.04 nM, respectively), as well as rat brain membranes ($K_d = 0.044$ nM). Potentially useful as a tool for autoradiographic studies of MCH distribution in the CNS.

SOURCE – Servier.

REFERENCES

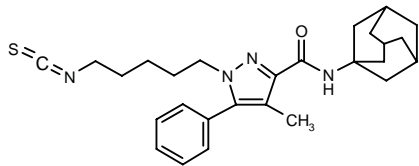
1. Audinot, V. et al. [¹²⁵I]-S36057: A new and highly potent radioligand for the melanin-concentrating hormone receptor. Br J Pharmacol 2001, 133(3): 371.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

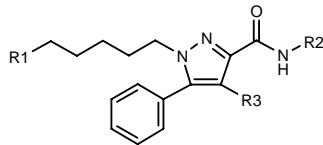
304081

N-(1-Adamantyl)-1-(5-isothiocyanatopentyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide



C27 H34 N4 O S; Mol wt: 462.6586

ACTION – Agent with preferential affinity for cannabinoid CB₂ receptors over CB₁ receptors (K_i = 0.507 and 5.76 nM, respectively), potentially useful for the treatment of pain, glaucoma, epilepsy, chemotherapy-associated nausea, neurodegenerative diseases, diseases associated with motor function, inflammation, mental disorders, to modulate appetite, to modulate the immune system, to produce vasoconstriction or vasodilatation and to enhance memory. Other compounds from this series of pyrazole derivatives include the following:



Compound	R1	R2	R3	Formula
304083	Cl	endo-1,7,7-(Me)3-bicyclo[2.2.1]hept-2-yl	Me	C ₂₆ H ₃₆ ClN ₃ O
304084	Cl	1-adamantyl	Me	C ₂₆ H ₃₄ ClN ₃ O
304086	Cl	2-Naph	Me	C ₂₆ H ₂₆ ClN ₃ O
304087	Cl	2-adamantyl	Me	C ₂₆ H ₃₄ ClN ₃ O
304089	Cl	1-adamantyl-CH ₂	Me	C ₂₇ H ₃₆ ClN ₃ O
304090	Cl	1-adamantyl	H	C ₂₅ H ₃₂ ClN ₃ O
304091	Cl	4,6,6-(Me)3-bicyclo[3.1.1]hept-2-yl	Me	C ₂₆ H ₃₆ ClN ₃ O
304092	Cl	6,6-(Me)2-bicyclo[3.1.1]hept-2-yl-CH ₂	Me	C ₂₆ H ₃₆ ClN ₃ O
304093	F	1-adamantyl	Me	C ₂₆ H ₃₄ FN ₃ O
304094	I	1-adamantyl	Me	C ₂₆ H ₃₄ IN ₃ O
304095	N3	1-adamantyl	Me	C ₂₆ H ₃₄ N ₆ O

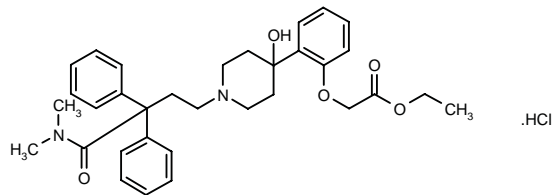
SOURCE – University of Connecticut, Storrs, CT (US).

REFERENCES

1. Makriyannis, A. and Liu, Q. (University of Connecticut) *Pyrazole derivs. as cannabinoid receptor antagonists*. WO 0129007.

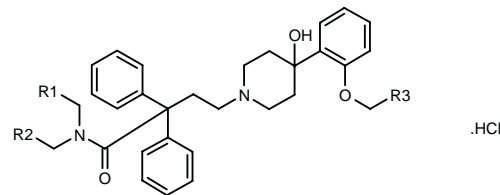
304434

2-[2-[1-[3-(*N,N*-Dimethylcarbamoyl)-3,3-diphenylpropyl]-4-hydroxypiperidin-4-yl]phenoxy]acetic acid ethyl ester hydrochloride



C33 H40 N2 O5 . HCl; Mol wt: 581.1489

ACTION – Peripheral analgesic agent, a mu opioid receptor agonist, as demonstrated in functional assays in guinea pig ileum, where it exhibited a relative potency of 8.3 compared to the selective mu opioid agonist DAMGO (potency = 1.0) and was more potent than morphine and loperamide (potency relative to DAMGO = 0.14 and 4.3, respectively). Compound was shown to cause loss of the righting reflex in 10-day-old rats at 0.3 pmol/kg s.c. Other exemplified compounds from this series of loperamide derivatives include the following:



Compound	R1	R2	R3	Formula
304435	H	H	CH ₂ OAc	C ₃₃ H ₄₀ N ₂ O ₅ .HCl
304436	H	H	CH ₂ OH	C ₃₁ H ₃₈ N ₂ O ₄ .HCl
304437	H	H	CH ₂ CH ₂ OH	C ₃₂ H ₄₀ N ₂ O ₄ .HCl
304438	H	H	(CH ₂) ₃ OH	C ₃₃ H ₄₂ N ₂ O ₄ .HCl
304439	H	H	CONH ₂	C ₃₁ H ₃₇ N ₃ O ₄ .HCl
304440	-(CH ₂) ₂ -		CO ₂ Et	C ₃₅ H ₄₂ N ₂ O ₅ .HCl
304441	H	H	CO ₂ H	C ₃₁ H ₃₆ N ₂ O ₅ .HCl

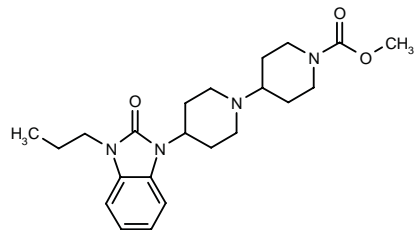
SOURCE – SSP.

REFERENCES

1. Mogi, K. et al. (SSP Co., Ltd.) *4-Hydroxy-4-phenylpiperidine derivs. having μ -opioid agonist activity and pharmaceuticals containing the same*. EP 1097924, JP 2001199959.

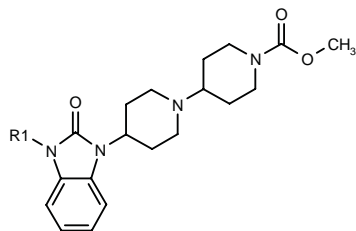
304447

4-(2-Oxo-3-propyl-2,3-dihydro-1*H*-benzimidazol-1-yl)-1,4'-bipiperidine-1'-carboxylic acid methyl ester



C22 H32 N4 O3; Mol wt: 400.5198

ACTION – Analgesic agent, also reported to be useful for the treatment of tolerance and addiction to narcotic analgesics such as morphine, itching, dementia, irritable bowel syndrome, schizophrenia, glaucoma, urinary incontinence, gallstones, cholecystitis, functional dyspepsia and reflux esophagitis, a muscarinic acetylcholine M₄ receptor agonist, as demonstrated in a luciferase reporter gene assay using CHO cells expressing the human receptor. *In vivo*, compound displayed a potent analgesic effect in the mouse tail-pinch test at 1 mg/kg s.c. Other compounds from this series of substituted imidazolidinone derivatives include the following:



Compound	R1	Formula
304448	Me	C ₂₀ H ₂₈ N ₄ O ₃
304449	Et	C ₂₁ H ₃₀ N ₄ O ₃
304450	SO ₂ Me	C ₂₀ H ₂₈ N ₄ O ₅ S
304451	CO ₂ Me	C ₂₁ H ₂₈ N ₄ O ₅

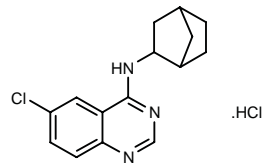
SOURCE – Banyu.

REFERENCES

1. Yamakawa, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Substd. imidazolidinone derivs*. WO 0127104.

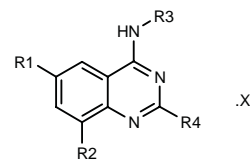
304758

N-(Bicyclo[2.2.1]hept-2-yl)-6-chloroquinazolin-4-amine hydrochloride

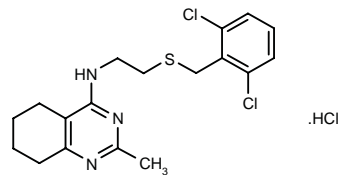


C15 H16 Cl N3 . HCl; Mol wt: 310.2263

ACTION – Agent for the treatment of pain and migraine, a selective group I metabotropic glutamate receptor type 1 (mGluR₁ or mglu₁) antagonist, as demonstrated *in vitro* by IC₅₀ values of 400 nM and 13,000 nM, respectively, for inhibition of quisqualate-stimulated phosphoinositide hydrolysis in mglu₁- and mglu₅-expressing cells. In addition, compound is reported to exhibit antinociceptive activity in the formalin, the Chung neuropathic pain and carrageenan-induced pain models, and it was found to be active in animal models of dural protein extravasation. Other exemplified compounds from this series of 4-substituted quinazoline derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
304759	H	Cl	bicyclo-[2.2.1]hept-2-yl	H	HCl	C ₁₅ H ₁₆ ClN ₃ .HCl
304760	OMe	H	4-MeO-Ph	H	HCl	C ₁₆ H ₁₅ N ₃ O ₂ .HCl
304761	OMe	H	2,6-(Cl)2-Ph-CH ₂ SCH ₂ CH ₂	H		C ₁₈ H ₁₇ Cl ₂ N ₃ OS
304762	Cl	H	bicyclo-[2.2.1]hept-2-yl	SCH ₂ CH ₂ OH	HCl	C ₁₇ H ₂₀ ClN ₃ OS.HCl
304763	OMe	H	4-MeO-Ph	SCH ₂ CH ₂ OH	HCl	C ₁₈ H ₁₉ N ₃ O ₃ S.HCl



304764: C18 H21 Cl2 N3 S . HCl

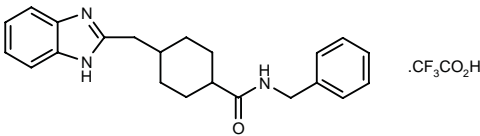
SOURCE – Lilly.

REFERENCES

1. Ambler, S.J. et al. (Eli Lilly and Company) *Pharmaceutical cpds*. WO 0132632.

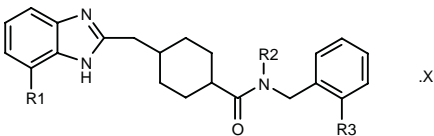
305050

4-(1*H*-Benzimidazol-2-ylmethyl)-*N*-benzylcyclohexane-carboxamide trifluoroacetate



C22 H25 N3 O . C2 H F3 O2; Mol wt: 461.4814

ACTION – Agent for the treatment of pain that acts as an NMDA NR2B subunit antagonist. The compound may also be useful for the treatment of depression, schizophrenia, Parkinson's disease and stroke. Other specifically claimed 2-cyclohexyl-benzimidazoles are:



Compound	R1	R2	R3	Isomer	X	Formula
305051	H	Me	H	cis	CF3CO2H	C ₂₃ H ₂₇ N ₃ O ₂ .C ₂ HF ₃ O ₂
305052	OH	H	H	cis	HCl	C ₂₂ H ₂₅ N ₃ O ₂ .HCl
305053	OH	H	F	cis	HCl	C ₂₂ H ₂₄ FN ₃ O ₂ .HCl
305054	OH	H	H	trans	HCl	C ₂₂ H ₂₅ N ₃ O ₂ .HCl
305055	OH	H	F	trans	HCl	C ₂₂ H ₂₄ FN ₃ O ₂ .HCl

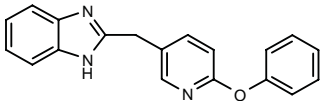
SOURCE – Merck & Co.

REFERENCES

1. Thompson, W. et al. (Merck & Co., Inc.) *2-Cyclohexyl benzimidazole NMDA/NR2B antagonists*. US 6291499, WO 0132634.

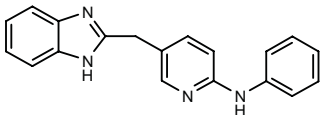
305056

2-(6-Phenoxypyridin-3-ylmethyl)-1*H*-benzimidazole



C19 H15 N3 O; Mol wt: 301.3475

ACTION – Agent for the treatment of pain that acts as an NMDA NR2B subunit antagonist. The compound may also be useful for the treatment of depression, schizophrenia, Parkinson's disease and stroke. Another specifically claimed benzimidazole is:



305057: C19 H16 N4

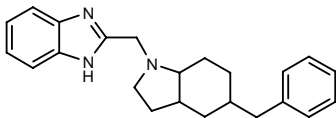
SOURCE – Merck & Co.

REFERENCES

1. McCauley, J.A. et al. (Merck & Co., Inc.) *2-Benzyl and 2-heteroaryl benzimidazole NMDA/NR2B antagonists*. WO 0132174.

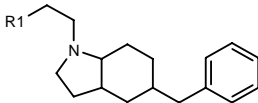
305058

2-(5-Benzylperhydroindol-1-ylmethyl)-1*H*-benzimidazole



C23 H27 N3; Mol wt: 345.4873

ACTION – Agent for the treatment of pain that acts as an NMDA NR2B subunit antagonist. The compound may also be useful for the treatment of depression, schizophrenia, Parkinson's disease and stroke. Other compounds from this series of octahydroindoles and decahydroquinolines are:



Compound	R1	Formula
305059	4-OH-PhO	C ₂₃ H ₂₉ NO ₂
305060	4-Cl-5-imidazolyl-CH2	C ₂₁ H ₂₆ ClN ₃
305061	2,4-(Cl)2-5-imidazolyl-CH2	C ₂₁ H ₂₇ Cl ₂ N ₃
305062	5-imidazolyl-CH2	C ₂₁ H ₂₉ N ₃
305063	4-imidazolyl	C ₂₀ H ₂₇ N ₃

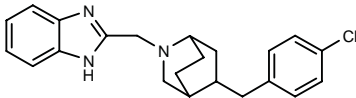
SOURCE – Merck & Co.

REFERENCES

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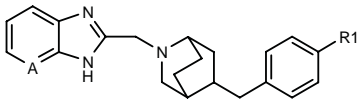
305064

2-[5-(4-Chlorobenzyl)-2-azabicyclo[2.2.2]oct-2-ylmethyl]-1*H*-benzimidazole



C22 H24 Cl N3; Mol wt: 365.9056

ACTION – Agent for the treatment of pain that acts as an NMDA NR2B subunit antagonist. The compound may also be useful for the treatment of depression, schizophrenia, Parkinson's disease and stroke. Other specifically claimed 2-azabicyclo[2.2.2]octanes are:



Compound	R1	A	Formula
305065	H	CH	C ₂₂ H ₂₅ N ₃
305066	Cl	N	C ₂₁ H ₂₃ ClN ₄
305067	H	N	C ₂₁ H ₂₄ N ₄

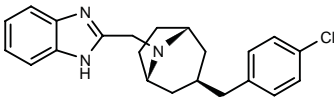
SOURCE – Merck & Co.

REFERENCES

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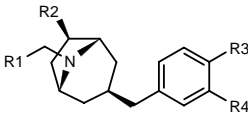
305068

exo-2-[3-(4-Chlorobenzyl)-8-azabicyclo[3.2.1]oct-8-ylmethyl]-1*H*-benzimidazole



C22 H24 Cl N3; Mol wt: 365.9056

ACTION – Agent for the treatment of pain that acts as an NMDA NR2B subunit antagonist. The compound may also be useful for the treatment of depression, schizophrenia, Parkinson’s disease and stroke. Other specifically claimed 8-azabicyclo[3.2.1]octanes are:



Compound	R1	R2	R3	R4	Formula
305069	2-benzimidazolyl	H	F	H	C ₂₂ H ₂₄ FN ₃
305070	2-benzimidazolyl	H	H	F	C ₂₂ H ₂₄ FN ₃
305071	2-benzimidazolyl	OH	H	H	C ₂₂ H ₂₅ N ₃ O
305073	4-OH-PhCH2CH2	H	Cl	H	C ₂₃ H ₂₆ ClNO
305074	2-benzimidazolyl-CH2CH2	H	H	H	C ₂₄ H ₂₉ N ₃
305075	1H-imidazo[4,5-c]pyridin-2-yl	H	H	H	C ₂₁ H ₂₄ N ₄

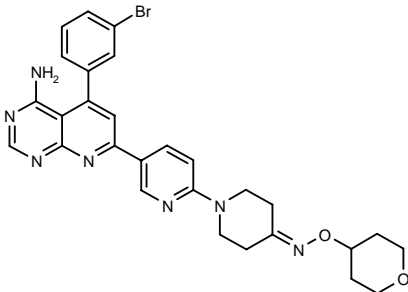
SOURCE – Merck & Co.

REFERENCES

1. Thompson, W. et al. (Merck & Co., Inc.) *8-Aza-bicyclo[3.2.1]octane NMDA/NR2B antagonists*. WO 0132179.

307203

1-[5-[4-Amino-5-(3-bromophenyl)pyrido[2,3-*d*]pyrimidin-7-yl]pyridin-2-yl]piperidin-4-one *O*-(tetrahydropyran-4-yl)-oxime



C28 H28 Br N7 O2; Mol wt: 574.4802

ACTION – Adenosine kinase inhibitor (IC₅₀ = 8 and 70.9 nM in enzymatic and whole-cell assays, respectively) with *in vivo* analgesic effects in a model of carrageenan-induced thermal hyperalgesia in rats (ED₅₀ = 1 μmol/kg p.o.). Compound showed an improved plasma half-life, higher oral bioavailability in rats and a better pharmacokinetic profile in dogs as compared to the parent compound ABT-702.

SOURCE – Abbott.

REFERENCES

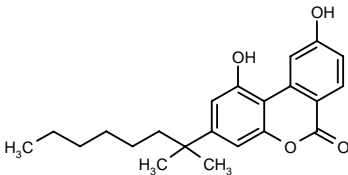
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AM-1714

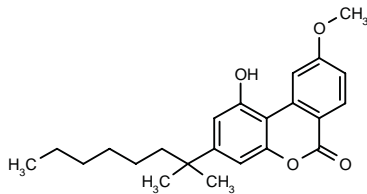
304075

3-(1,1-Dimethylheptyl)-1,9-dihydroxy-6*H*-dibenzo-[*b,d*]pyran-6-one



C22 H26 O4; Mol wt: 354.4434

ACTION – Agent with preferential affinity for the cannabinoid CB₂ receptor over CB₁ receptors, potentially useful for the treatment of pain, glaucoma, epilepsy, chemotherapy-associated nausea, neurodegenerative diseases, diseases associated with motor function and inflammation. *In vivo*, compound was shown to elicit notable analgesic effects in rat models of thermal hyperalgesia when administered i.p. or by intraplantar injection, effects which were blocked by the selective CB₂ antagonist AM-630 but not by the selective CB₁ antagonist AM-251. Another compound from this series of polycyclic cannabinoid analogues is:



AM-1710 [304462]: C23 H28 O4

SOURCE – University of Connecticut, Storrs, CT (US).

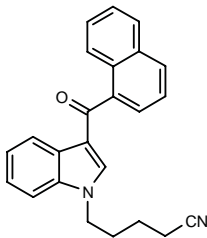
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AM-2232

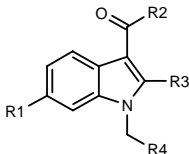
304077

5-[3-(Naphthalen-1-ylcarbonyl)-1*H*-indol-1-yl]pentane-nitrile



C24 H20 N2 O; Mol wt: 352.4350

ACTION – Agent with high affinity for cannabinoid CB₁ and CB₂ receptors (K_i = 0.28 and 1.48 nM, respectively), potentially useful for the treatment of pain, glaucoma, epilepsy, chemotherapy-associated nausea, neurodegenerative diseases, diseases associated with motor function, inflammation, mental disorders, to modulate appetite, to modulate the immune system, to produce vasoconstriction or vasodilatation and to enhance memory. Other compounds from this series of indole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
AM-1224 [304078]	N3	1-Naph	H	1-Me-2-Pip	C ₂₆ H ₂₆ N ₅ O
AM-1221 [304464]	NO2	1-Naph	Me	1-Me-2-Pip	C ₂₇ H ₂₇ N ₃ O ₃
AM-694 [304466]	H	2-I-Ph	H	(CH ₂) ₄ F	C ₂₀ H ₁₉ FINO
AM-2201 [304468]	H	1-Naph	H	(CH ₂) ₄ F	C ₂₄ H ₂₂ FNO
AM-1230 [304469]	I	1-Naph	H	(CH ₂) ₄ F	C ₂₄ H ₂₁ FINO

SOURCE – University of Connecticut, Storrs, CT (US).

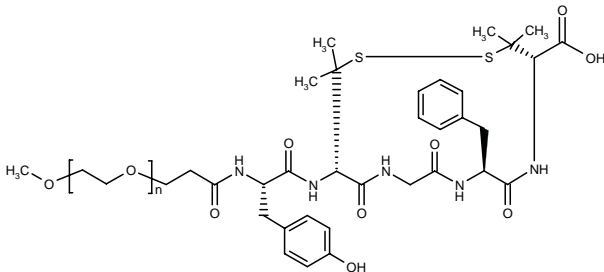
REFERENCES

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PEG-DPDPE

307286

N-[3-(*O*-Methylpoly(ethylene glycol)propionyl]-L-tyrosyl-D-penicillaminy-glycyl-L-phenylalanyl-D-penicillamine cyclic disulfide



C34 H45 N5 O9 S2(C2 H4 O)n

ACTION – Polyethylene glycol (PEG)-conjugated met-enkephalin analogue that appears to act as a prodrug, enhancing the peripheral pharmacokinetic profile and improving the analgesic effect in mice after i.v. administration compared with the unconjugated form. In brain, the conjugate was hydrolyzed to DPDPE, which interacts with the delta opioid receptor with 172-fold greater affinity than the conjugate. The conjugate showed increased hydrophilicity and a longer elimination half-life whereas volume of distribution and plasma clearance rate were decreased. Potentially useful as an analgesic agent.

SOURCES – University of Arizona, Tucson, AZ (US); Shearwater.

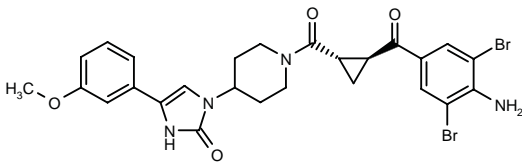
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ANTIMIGRAINE DRUGS

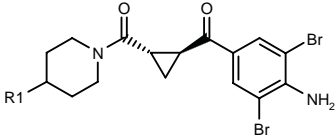
305089

trans-1-[1-[2-(4-Amino-3,5-dibromobenzoyl)cyclopropyl-carbonyl]piperidin-4-yl]-4-(3-methoxyphenyl)-2,3-dihydro-1*H*-imidazol-2-one



C26 H26 Br2 N4 O4; Mol wt: 618.3234

ACTION – Calcitonin gene-related peptide (CGRP) antagonist expected to be useful for the treatment or prevention of headache, especially migraine, as well as non-insulin-dependent diabetes mellitus, cardiovascular disorders, skin disorders, inflammatory disorders, allergic rhinitis, asthma and menopausal flushes. Other specifically claimed *trans*-cyclopropanes are:



Compound	R1	Formula
305090	2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	C ₂₄ H ₂₄ Br ₂ N ₄ O ₃
305091	2-oxo-4-(3-Ph-2,3-dihydro-1-imidazolyl)	C ₂₅ H ₂₄ Br ₂ N ₄ O ₃
305092	2-oxo-4-(3-OH-Ph)-2,3-dihydro-1-imidazolyl	C ₂₅ H ₂₄ Br ₂ N ₄ O ₄
305093	6-OH-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	C ₂₄ H ₂₄ Br ₂ N ₄ O ₄
305094	6-(1,3-dioxolan-2-yl-CH ₂ O)-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	C ₂₈ H ₃₀ Br ₂ N ₄ O ₆
305095	4-(3-Cl-Ph)-2-oxo-2,3-dihydro-1-imidazolyl	C ₂₅ H ₂₃ Br ₂ ClN ₄ O ₃
305096	6-[N(Me)2(CH2)3O]-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	C ₂₉ H ₃₅ Br ₂ N ₅ O ₄
305097	6-(CO ₂ MeCH ₂ O)-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	C ₂₇ H ₂₈ Br ₂ N ₄ O ₆
305098	6-(CO ₂ HCH ₂ O)-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	C ₂₆ H ₂₆ Br ₂ N ₄ O ₆
305099	3-Ph-5-oxo-4,5-dihydro-1,2,4-triazol-1-yl	C ₂₄ H ₂₃ Br ₂ N ₅ O ₃

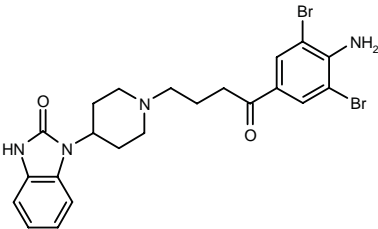
SOURCE – Boehringer Ingelheim.

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1. Eberlein, W. et al. (Boehringer Ingelheim Pharma KG) *Novel cyclopropanes as CGRP antagonists, medicaments containing said cpds. and method for the production thereof.* DE 19952147, WO 0132648.

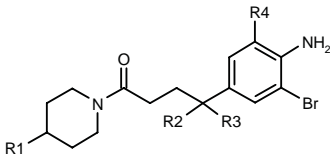
305100

1-[1-[4-(4-Amino-3,5-dibromophenyl)-4-oxobutyl]piperidin-4-yl]-2,3-dihydro-1*H*-benzimidazol-2-one

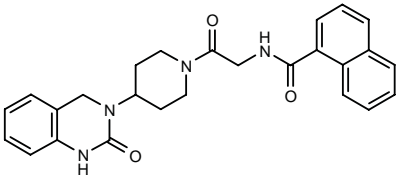


C22 H24 Br2 N4 O2; Mol wt: 536.2656

ACTION – Calcitonin gene-related peptide (CGRP) antagonist expected to be useful for the treatment or prevention of headache, especially migraine, as well as non-insulin-dependent diabetes mellitus, cardiovascular disorders, skin disorders, inflammatory disorders, allergic rhinitis, asthma and menopausal flushes. Other compounds from this series of arylalkanes, arylalkenes and arylazaalkanes are:



Compound	R1	R2	R3	R4	Formula
305101	2-oxo-2,3-dihydro-1-benzimidazolyl	-O-		H	C ₂₂ H ₂₃ Br ₂ N ₄ O ₃
305102	2-oxo-1,2,3,4-tetrahydro-thieno[3,2-d]pyrimidin-3-yl	-O-		Br	C ₂₁ H ₂₂ Br ₂ N ₄ O ₃ S
305103	2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	H	H	Br	C ₂₃ H ₂₆ Br ₂ N ₄ O ₂
305104	OH	-O-		Br	C ₁₅ H ₁₈ Br ₂ N ₂ O ₃
305105	4-[3,5-(Br)2-4-NH2-Ph]-2-oxo-2,3-dihydro-1 <i>H</i> -1-imidazolyl	-O-		Br	C ₂₄ H ₂₃ Br ₄ N ₅ O ₃
305106	7-(NH ₂ CO)-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	-O-		Br	C ₂₄ H ₂₅ Br ₂ N ₅ O ₄
305109	6-Cl-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl	-O-		Br	C ₂₃ H ₂₃ Br ₂ ClN ₄ O ₃
305110	2-(<i>t</i> -BuOCO ₂ H)-3,4-dihydro-3-quinazolinyl	-O-		Br	C ₂₈ H ₃₃ Br ₂ N ₅ O ₄



305108: C26 H26 N4 O3

SOURCE – Boehringer Ingelheim.

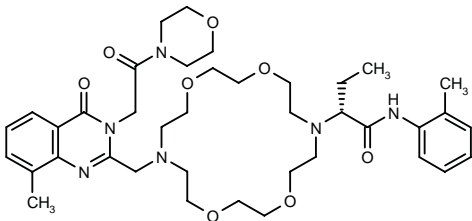
REFERENCES

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ANESTHETIC DRUGS

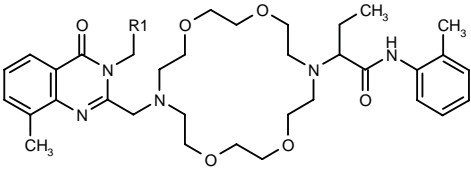
303653

2(*R*)-[16-[8-Methyl-3-[2-(4-morpholinyl)-2-oxoethyl]-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl]-*N*-(2-methylphenyl)-butyramide

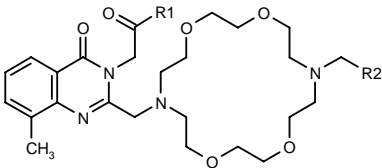


C39 H56 N6 O8; Mol wt: 736.9054

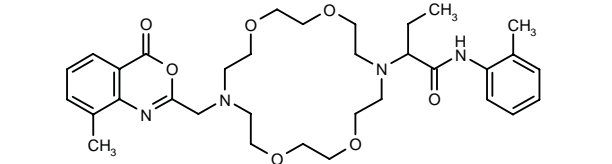
ACTION – Voltage-gated sodium channel blocker, potentially useful as a local anesthetic, as well as for the treatment or prevention of depression, epilepsy, stroke, ischemia, asthma, rapid heartbeat, cardiac arrhythmia, natriuresis, proctitis, inflammatory bowel disease and irritable bowel syndrome. Compound is reported to exhibit improved properties when compared with conventional local anesthetics such as lidocaine and bupivacaine such as a longer duration of action or reduced side effects. Other exemplified compounds from this series of quinazolinones and analogues are:



Compound	R1	Isomer	Formula
303655	4-morpholinyl-CO	racemic	C ₃₉ H ₅₆ N ₆ O ₈
303657	CH(OH)CH ₂ OH	racemic	C ₃₆ H ₅₃ N ₅ O ₈
303658	2-Pyr	racemic	C ₃₉ H ₅₂ N ₆ O ₈
303663	5-Me-2-pyrazinyl	racemic	C ₃₉ H ₅₃ N ₇ O ₆



Compound	R1	R2	Formula
303659	N(Me) ₂	8-Me-4-oxo-3-[N(Me) ₂ COCH ₂]-3,4-dihydro-2-quinazolinyl	C ₄₀ H ₅₆ N ₈ O ₈
303661	4-morpholinyl	2,4,6-(Me) ₃ -PhNHCO	C ₃₉ H ₅₆ N ₆ O ₈



303656: C33 H46 N4 O7

SOURCE – Advanced Medicine.

REFERENCES

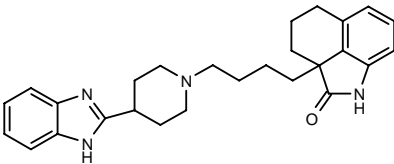
1. Axt, S.A. et al. (Advanced Medicine, Inc.) *Quinazolinones and analogues and their use as local anesthetics*. WO 0125234, WO 0125235.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

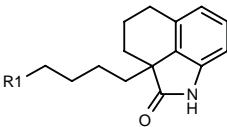
304194

2a-[4-[4-(1*H*-Benzimidazol-2-yl)piperidin-1-yl]butyl]-1,2,2a,3,4,5-hexahydrobenzo[*ca*]indol-2-one



C27 H32 N4 O; Mol wt: 428.5768

ACTION– 5-HT₇ receptor antagonist with potential for the treatment or prevention of a broad range of disorders including anxiety, depression, obsessive–compulsive disorder, schizophrenia, attention deficit disorders, sleep disorders, migraine, neurodegenerative disorders, pain, eating disorders, sexual dysfunction, ocular disorders, asthma, epilepsy, hypothalamic diseases, inflammation, renal disorders, hypotension, stroke, septic shock and gastrointestinal diseases. Other specifically claimed compounds from this series of tetrahydrobenzindolone derivatives are:



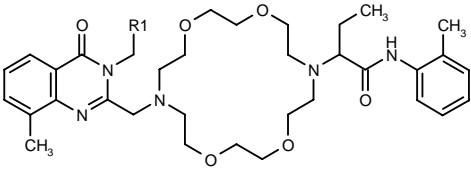
Compound	R1	Formula
304195	4-(5-Me-2-benzimidazolyl)-1-Pip	C ₂₈ H ₃₄ N ₄ O
304196	4-(2-benzoxazolyl)-1-Pip	C ₂₇ H ₃₁ N ₃ O ₂
304197	4-(2-benzothiazolyl)-1-Pip	C ₂₇ H ₃₁ N ₃ OS
304198	4-(2-benzimidazolyl)-1-Piz	C ₂₆ H ₃₁ N ₅ O
304199	4-(5-F-2-benzimidazolyl)-1-Piz	C ₂₆ H ₃₀ FN ₅ O
304200	4-(5-F-2-benzimidazolyl)-1-Piz-CH ₂	C ₂₇ H ₃₂ FN ₅ O
304201	4-(2-benzothiazolyl)-1-Piz	C ₂₆ H ₃₀ N ₄ OS
304202	4-(2-benzoxazolyl)-1-Piz	C ₂₆ H ₃₀ N ₄ O ₂
304203	4-(2-benzimidazolyl)-1,2,3,6-tetrahydro-1-Pyr	C ₂₇ H ₃₀ N ₄ O
304204	4-(2-indolyl)-1-Pip	C ₂₈ H ₃₃ N ₃ O

SOURCE – GlaxoSmithKline.

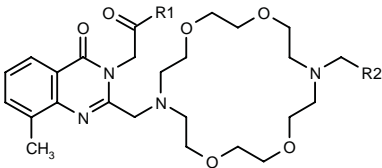
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1. Bromidge, S.M. et al. (SmithKline Beecham plc) *Tetrahydrobenzindolone derivs., their preparation and their use as 5-HT₇ receptor antagonists*. WO 0129029.

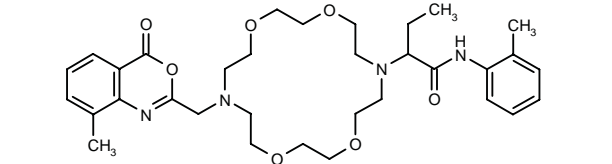
ACTION – Voltage-gated sodium channel blocker, potentially useful as a local anesthetic, as well as for the treatment or prevention of depression, epilepsy, stroke, ischemia, asthma, rapid heartbeat, cardiac arrhythmia, natriuresis, proctitis, inflammatory bowel disease and irritable bowel syndrome. Compound is reported to exhibit improved properties when compared with conventional local anesthetics such as lidocaine and bupivacaine such as a longer duration of action or reduced side effects. Other exemplified compounds from this series of quinazolinones and analogues are:



Compound	R1	Isomer	Formula
303655	4-morpholinyl-CO	racemic	C ₃₉ H ₅₆ N ₆ O ₈
303657	CH(OH)CH ₂ OH	racemic	C ₃₆ H ₅₃ N ₅ O ₈
303658	2-Pyr	racemic	C ₃₉ H ₅₂ N ₆ O ₈
303663	5-Me-2-pyrazinyl	racemic	C ₃₉ H ₅₃ N ₇ O ₆



Compound	R1	R2	Formula
303659	N(Me) ₂	8-Me-4-oxo-3-[N(Me) ₂ COCH ₂]-3,4-dihydro-2-quinazolinyl	C ₄₀ H ₅₆ N ₈ O ₈
303661	4-morpholinyl	2,4,6-(Me) ₃ -PhNHCO	C ₃₉ H ₅₆ N ₆ O ₈



303656: C33 H46 N4 O7

SOURCE – Advanced Medicine.

REFERENCES

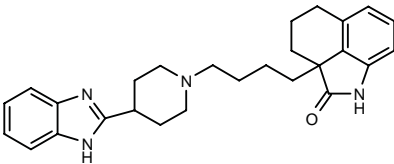
1. Axt, S.A. et al. (Advanced Medicine, Inc.) *Quinazolinones and analogues and their use as local anesthetics*. WO 0125234, WO 0125235.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

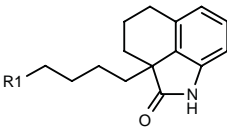
304194

2a-[4-[4-(1*H*-Benzimidazol-2-yl)piperidin-1-yl]butyl]-1,2,2a,3,4,5-hexahydrobenzo[*ca*]indol-2-one



C27 H32 N4 O; Mol wt: 428.5768

ACTION– 5-HT₇ receptor antagonist with potential for the treatment or prevention of a broad range of disorders including anxiety, depression, obsessive–compulsive disorder, schizophrenia, attention deficit disorders, sleep disorders, migraine, neurodegenerative disorders, pain, eating disorders, sexual dysfunction, ocular disorders, asthma, epilepsy, hypothalamic diseases, inflammation, renal disorders, hypotension, stroke, septic shock and gastrointestinal diseases. Other specifically claimed compounds from this series of tetrahydrobenzindolone derivatives are:



Compound	R1	Formula
304195	4-(5-Me-2-benzimidazolyl)-1-Pip	C ₂₈ H ₃₄ N ₄ O
304196	4-(2-benzoxazolyl)-1-Pip	C ₂₇ H ₃₁ N ₃ O ₂
304197	4-(2-benzothiazolyl)-1-Pip	C ₂₇ H ₃₁ N ₃ OS
304198	4-(2-benzimidazolyl)-1-Piz	C ₂₆ H ₃₁ N ₅ O
304199	4-(5-F-2-benzimidazolyl)-1-Piz	C ₂₆ H ₃₀ FN ₅ O
304200	4-(5-F-2-benzimidazolyl)-1-Piz-CH ₂	C ₂₇ H ₃₂ FN ₅ O
304201	4-(2-benzothiazolyl)-1-Piz	C ₂₆ H ₃₀ N ₄ OS
304202	4-(2-benzoxazolyl)-1-Piz	C ₂₆ H ₃₀ N ₄ O ₂
304203	4-(2-benzimidazolyl)-1,2,3,6-tetrahydro-1-Pyr	C ₂₇ H ₃₀ N ₄ O
304204	4-(2-indolyl)-1-Pip	C ₂₈ H ₃₃ N ₃ O

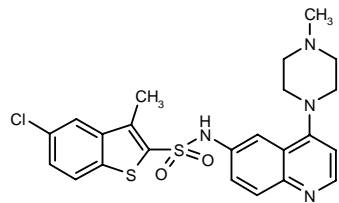
SOURCE – GlaxoSmithKline.

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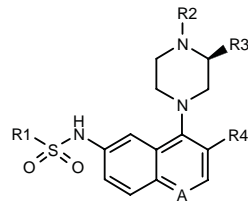
304841

5-Chloro-3-methyl-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]benzo[*b*]thiophene-2-sulfonamide



C23 H23 Cl N4 O2 S2; Mol wt: 487.0457

ACTION – Agent for the treatment of CNS disorders such as anxiety, depression, memory disorders, schizophrenia or attention deficit hyperactivity disorder, a 5-HT₆ receptor antagonist. Other bicyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
304842	3,5-(Cl)2-Ph	H	H	H	N	C ₁₉ H ₁₈ Cl ₂ N ₄ O ₂ S
304844	2-dibenzofuryl	H	H	H	N	C ₂₅ H ₂₂ N ₄ O ₃ S
304846	5,7-(Cl)2-2-Me-3-benzothieryl	H	H	H	N	C ₂₂ H ₂₀ Cl ₂ N ₄ O ₂ S ₂
304847	4-Cl-2,5-(Me)2-Ph	H	H	H	N	C ₂₁ H ₂₃ ClN ₄ O ₂ S
304848	4-I-Ph	H	H	H	N	C ₁₉ H ₁₉ IN ₄ O ₂ S
304849	5,7-(Cl)2-3-Me-2-benzothieryl	H	H	Me	N	C ₂₃ H ₂₂ Cl ₂ N ₄ O ₂ S ₂
304851	4-t-Bu-Ph	-(CH2)3-	H	N		C ₂₆ H ₃₂ N ₄ O ₂ S
304852	5-Cl-3-Me-2-benzothieryl	Me	H	H	CH	C ₂₄ H ₂₄ ClN ₃ O ₂ S ₂

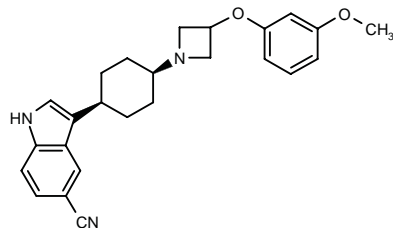
SOURCE – GlaxoSmithKline.

REFERENCES

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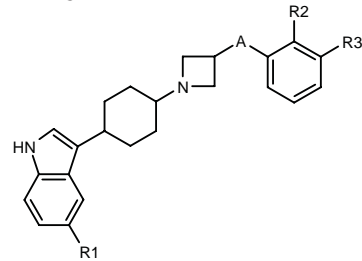
305001^{1,2}

cis-3-[4-[3-(3-Methoxyphenoxy)azetidin-1-yl]cyclohexyl]-1*H*-indole-5-carbonitrile



C25 H27 N3 O2; Mol wt: 401.5073

ACTION – Agent for the treatment of anxiety and depression with high affinity for the 5-HT transporter, as demonstrated by a K_i value of 2.38 nM against [³H]-paroxetine binding in rat frontal cortical membranes and by an IC₅₀ value of 91 nM for inhibition of [³H]-5-HT uptake by human carcinoma cells expressing the human 5-HT transporter. Other exemplified compounds from this series of 1-[(indol-3-yl)cycloalkyl]-3-substituted azetidines include the following:



Compound	R1	R2	R3	A	Isomer	Formula
305002 ²	F	OMe	H	NH	cis	C ₂₄ H ₂₈ FN ₃ O
305003 ²	F	OMe	H	NH	trans	C ₂₄ H ₂₈ FN ₃ O
305004 ²	CN	H	F	O	cis	C ₂₄ H ₂₄ FN ₃ O
305005 ²	CN	H	OMe	O	trans	C ₂₅ H ₂₇ N ₃ O ₂
305008 ²	F	H	F	NH	cis	C ₂₃ H ₂₅ F ₂ N ₃

SOURCE – American Home Products.

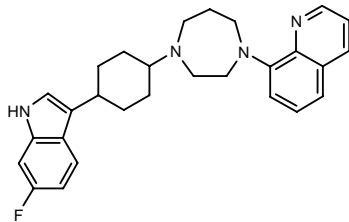
REFERENCES

1. Asselin, M. et al. (American Home Products Corp.) *[(Indol-3-yl)-cycloalkyl]-3-substd. azetidines for the treatment of central nervous system disorders.* US 6245799.

2. Asselin, M. et al. (American Home Products Corp.) *[(Indol-3-yl)-cycloalkyl]-3-substd. azetidines for the treatment of central nervous system disorders.* WO 0134598.

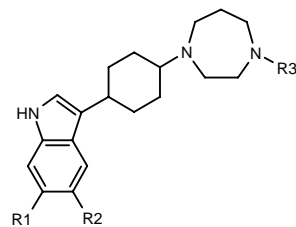
305011

8-[4-[4-(6-Fluoro-1*H*-indol-3-yl)cyclohexyl]perhydro-1,4-diazepin-1-yl]quinoline



C28 H31 F N4; Mol wt: 442.5789

ACTION – Agent for the treatment of anxiety and depression with high affinity for the 5-HT transporter, as demonstrated by a K_i value of 2.7 nM against [³H]-paroxetine binding in rat frontal cortical membranes and by an IC₅₀ value of 317 nM for inhibition of [³H]-5-HT uptake by human carcinoma cells expressing the human 5-HT transporter. Other specifically claimed compounds from this series of *N*-aryl-(homopiperaziny)-cyclohexyl amines are:



Compound	R1	R2	R3	Formula
305014	H	H	2-MeO-Ph	C ₂₆ H ₃₃ N ₃ O
305016	H	H	8-quinolyl	C ₂₈ H ₃₂ N ₄
305018	H	F	2-MeO-Ph	C ₂₆ H ₃₂ FN ₃ O
305019	H	CN	2-MeO-Ph	C ₂₇ H ₃₂ N ₄ O
305021	F	H	2-MeO-Ph	C ₂₆ H ₃₂ FN ₃ O
305023	H	F	8-quinolyl	C ₂₈ H ₃₁ FN ₄
305025	H	CN	8-quinolyl	C ₂₉ H ₃₁ N ₅
305027	H	F	3-CF3-Ph	C ₂₆ H ₂₉ F ₄ N ₃
305028	H	CN	3-CF3-Ph	C ₂₇ H ₂₉ F ₃ N ₄
305029	F	H	3-CF3-Ph	C ₂₆ H ₂₉ F ₄ N ₃

SOURCE – American Home Products.

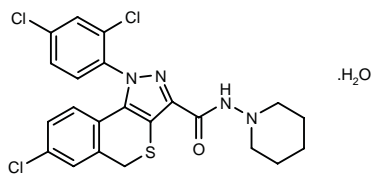
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1. Gilbert, A.M. and Mewshaw, R.E. (American Home Products Corp.) *N*-Aryl-(homopiperazinyl)-cyclohexyl amines as 5-HT transporters. WO 0134597.

ANTIPSYCHOTIC DRUGS

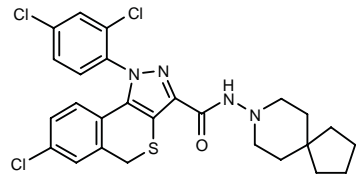
304735

7-Chloro-1-(2,4-dichlorophenyl)-*N*-(1-piperidinyl)-1,5-dihydro[2]benzothiopyrano[4,3-*c*]pyrazole-3-carboxamide hydrate



C22 H19 Cl3 N4 O S . H2O; Mol wt: 511.8589

ACTION – Selective cannabinoid CB₁ receptor antagonist, potentially useful for the treatment of CB₁-mediated disorders such as psychotic disorders, schizophrenia, eating disorders, obesity and cognitive and memory disorders. Another exemplified compound from this series of tricyclic pyrazolecarboxylic acid derivatives is:



304736: C26 H25 Cl3 N4 O S

SOURCE – Sanofi-Synthélabo.

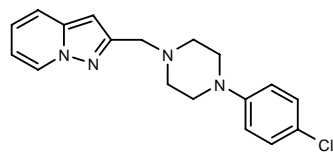
REFERENCES

1. Barth, F. et al. (Sanofi-Synthélabo) *Pyrazolecarboxylic acid tricyclic derivs., preparation and pharmaceutical compsns. containing same.* FR 2800375, WO 0132663.

FAUC-213

306505

2-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo-[1,5-*a*]pyridine



C18 H19 Cl N4; Mol wt: 326.8291

ACTION – Dopamine D4 receptor antagonist with nanomolar affinity and high selectivity for the human D4.4 receptor versus bovine D1, human D2long, D2short and D3 receptors (K_i = 2.2, 5500, 3400, 6300 and 5300 nM, respectively). In an *in vitro* functional assay of ligand-induced mitogenesis, compound exhibited complete antagonist properties similar to those of clozapine. Potentially useful as an atypical antipsychotic agent.

SOURCE – Friedrich-Alexander-Universität, Erlangen (DE).

REFERENCES

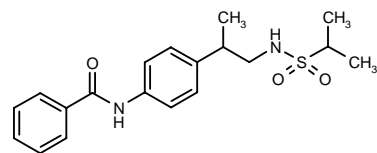
1. Lanig, H. et al. *Comparative molecular field analysis of dopamine D4 receptor antagonists including 3-[4-(4-chlorophenyl) piperazin-1-ylmethyl]pyrazolo[1,5-a]pyridine (FAUC 113), 3-[4-chlorophenyl]piperazin-1-ylmethyl]-1H-pyrrolo-[2,3-b]pyridine (L-745,870), and clozapine.* J Med Chem 2001, 44(8): 1151.

2. Löber, S. et al. *Rationally based efficacy tuning of selective dopamine D4 receptor ligands leading to the complete antagonist 2-[4-(4-chlorophenyl) piperazin-1-ylmethyl]pyrazolo[1,5-a]pyridine (FAUC 213).* J Med Chem 2001, 44(17): 2691.

LY-395153*

298907

N-[4-[2-(Isopropylsulfonamido)-1-methylethyl]phenyl]-benzamide



C19 H24 N2 O3 S; Mol wt: 360.4756

ACTION – AMPA receptor potentiator proven to increase AMPA receptor-mediated inward currents in isolated cerebellar Purkinje neurons. [³H]-Labeled compound is a high-affinity radioligand for a putative AMPA receptor potentiator site. Potentially useful for the treatment of neuropsychiatric disorders including memory impairment and schizophrenia, and also as a tool.

SOURCE – Lilly.

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2. Arnold, M.B. et al. (Eli Lilly and Company) *Sulphonamide derivs.* EP 0860428, JP 2001511781, WO 9833496.

3. Linden, A.M. et al. *Binding of an AMPA receptor potentiator ([3H]LY395153) to native and recombinant AMPA receptors.* Neuropharmacology 2001, 40(8): 1010.

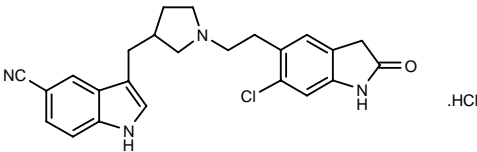
4. Zarrinmayed, H. et al. *[3H]N-2-(4-Benzamido)phenyl)propyl-2-propanesulfonamide: A novel AMPA receptor potentiator and radioligand.* J Med Chem 2001, 44(3): 302.

*Identified compound **298907** Drug Data Rep 2001, 023(04): 0422.

TREATMENT OF MOOD DISORDERS

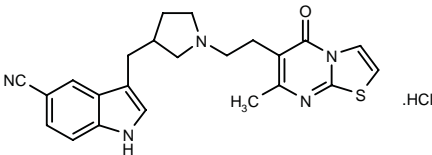
303641

3-[1-[2-(6-Chloro-2-oxo-2,3-dihydro-1 *H*-indol-5-yl)ethyl]-pyrrolidin-3-ylmethyl]-1 *H*-indole-5-carbonitrile hydrochloride



C24 H23 Cl N4 O . HCl; Mol wt: 455.3866

ACTION – 5-HT reuptake inhibitor (K_i = 0.4 nM against [³H]-paroxetine binding in rat frontal cortex preparations), potentially useful for the treatment of depression, panic attacks, obsessive–compulsive disorders, phobia, drug abuse and anxiety. Another specifically claimed compound from this series of cyanoindole derivatives is:



303643: C23 H23 N5 O S . HCl

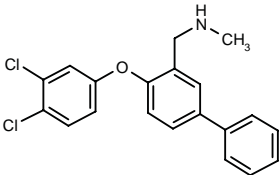
SOURCE – ADIR.

REFERENCES

1. Lavielle, G. et al. (ADIR et Cie.) *Cyano-indole derivs. as inhibitors of serotonin reuptake, method for their preparation and pharmaceutical compsns. containing the same.* EP 1092715, FR 2799463, JP 2001151772.

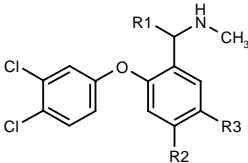
303933

N-[4-(3,4-Dichlorophenoxy)biphenyl-3-ylmethyl]-*N*-methylamine



C20 H17 Cl2 N O; Mol wt: 358.2663

ACTION – An inhibitor of 5-HT, noradrenaline and dopamine reuptake (IC_{50} = 250, 1000 and 1000 nM or less, respectively), potentially useful for the treatment of depression, hypertension, anxiety, phobias, posttraumatic stress syndrome, premature ejaculation, eating disorders, obesity, chemical dependencies, migraine, pain, Alzheimer's disease, obsessive–compulsive disorder, panic disorder, memory disorders, Parkinson's disease, endocrine disorders, vasospasm, gastrointestinal tract disorders, premenstrual syndrome and attention deficit hyperactivity disorder, among others. Other specifically claimed compounds from this series of biaryl ether derivatives include the following:



Compound	R1	R2	R3	Formula
303934	H	2-furyl	H	C ₁₈ H ₁₅ Cl ₂ NO ₂
303935	H	H	4-F-Ph	C ₂₀ H ₁₆ Cl ₂ FNO
303936	H	H	2-Pyr	C ₁₉ H ₁₆ Cl ₂ N ₂ O
303937	H	H	4-Pyr	C ₁₉ H ₁₆ Cl ₂ N ₂ O
303938	H	H	2-thiazolyl	C ₁₇ H ₁₄ Cl ₂ N ₂ OS
303939	Me	H	2H-1,2,3-triazol-2-yl	C ₁₇ H ₁₆ Cl ₂ N ₄ O
303940	H	H	1,2,4-triazol-4-yl	C ₁₈ H ₁₄ Cl ₂ N ₄ O
303941	H	H	2-oxo-1-Pip	C ₁₉ H ₂₀ Cl ₂ N ₂ O ₂

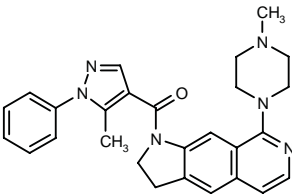
SOURCE – Pfizer.

REFERENCES

1. Howard, H.R. Jr. and Adam, M.D. (Pfizer Products Inc.) *Biaryl ether derivs. useful as monoamine reuptake inhibitors.* WO 0127068.

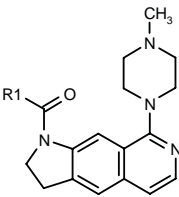
304766

1-(5-Methyl-1-phenyl-1 *H*-pyrazol-4-yl)-1-[8-(4-methyl-piperazin-1-yl)-2,3-dihydro-1 *H*-pyrrolo[3,2-*g*]isoquinolin-1-yl]methanone



C27 H28 N6 O; Mol wt: 452.5592

ACTION – Combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor ligand with potential for the treatment or prophylaxis of CNS disorders, particularly depression. Other specifically claimed compounds from this series of isoquinoline and quinazoline derivatives are:



Compound	R1	Formula
304767	2-F-Ph	C ₂₃ H ₂₃ FN ₄ O
304768	1-(4-CN-Ph)-5-Et-4-pyrazolyl	C ₂₉ H ₂₉ N ₇ O
304769	1-(4-CN-Ph)-5-Me-4-pyrazolyl	C ₂₈ H ₂₇ N ₇ O
304770	4-Et-2-Me-5-oxazolyl	C ₂₃ H ₂₇ N ₅ O ₂

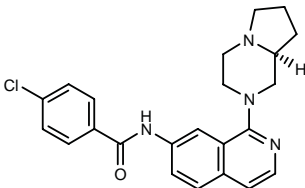
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gaster, L.M. et al. (SmithKline Beecham plc) *Isoquinoline and quinazoline derivs. having a combined 5HT_{1A}, 5HT_{1B} and 5HT_{1D} receptor activity.* WO 0132626.

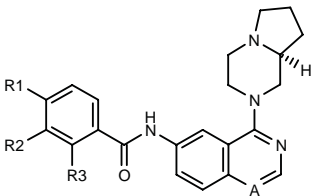
304771

(–)-4-Chloro-*N*-[1-[(8*aS*)-perhydropyrrolo[1,2-*a*]pyrazin-2-yl]isoquinolin-7-yl]benzamide



C23 H23 Cl N4 O; Mol wt: 406.9147

ACTION – Combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor ligand with potential for the treatment or prophylaxis of CNS disorders, particularly depression. Other specifically claimed compounds from this series of isoquinoline and quinazoline derivatives are:



Compound	R1	R2	R3	A	Formula
304772	Cl	Cl	H	CH	C ₂₃ H ₂₂ Cl ₂ N ₄ O
304773	H	H	Cl	N	C ₂₂ H ₂₂ ClN ₅ O

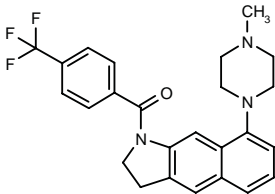
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gaster, L.M. and Heightman, T.D. (SmithKline Beecham plc) *Isoquinoline and quinazoline derivs. for the treatment of CNS disorders.* WO 0132659.

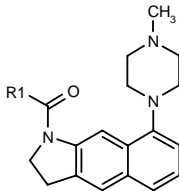
304774

1-[8-(4-Methylpiperazin-1-yl)-2,3-dihydro-1*H*-benz[*f*]-indol-1-yl]-1-[4-(trifluoromethyl)phenyl]methanone



C25 H24 F3 N3 O; Mol wt: 439.4786

ACTION – Combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor ligand with potential for the treatment or prophylaxis of CNS disorders, particularly depression. Other specifically claimed compounds from this series of benz[*f*]indole derivatives are:



Compound	R1	Formula
304776	2,4-(Cl)2-Ph	C ₂₄ H ₂₃ Cl ₂ N ₃ O
304777	4-EtO-Ph	C ₂₆ H ₂₉ N ₃ O ₂
304778	5-Cl-2-thienyl	C ₂₂ H ₂₂ ClN ₃ OS

SOURCE – GlaxoSmithKline.

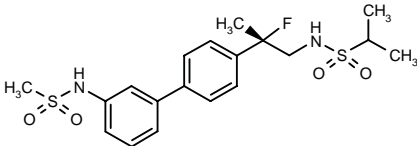
REFERENCES

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LY-503429

307496

N-[2(*S*)-Fluoro-2-[3'-(methylsulfonamido)biphenyl-4-yl]-propyl]propane-2-sulfonamide



C19 H25 F N2 O4 S2; Mol wt: 428.5465

ACTION – AMPA receptor potentiator (EC₅₀ = 10.9 nM) active in preclinical models predictive of antidepressant activity.

SOURCE – Lilly.

REFERENCES

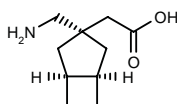
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2. Zarrinmayeh, H. et al. *AMPA receptor potentiators as potentially novel antidepressants.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 303.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

304123

(1 α ,3 α ,5 α)-2-[3-(Aminomethyl)bicyclo[3.2.0]hept-3-yl]-acetic acid



C10 H17 N O2; Mol wt: 183.2493

ACTION – A representative compound from a series of bicyclic amino acids with activity similar to gabapentin. This compound demonstrated binding to the calcium channel α_2 - δ subunit (IC_{50} = 0.038 μ M using [3 H]-gabapentin as the radioligand and porcine brain tissue) and is potentially useful for the treatment of epilepsy, faintness attacks, hypokinesia, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders and premenstrual syndrome.

SOURCE – Pfizer.

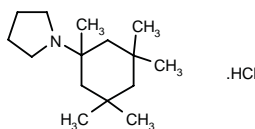
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1. Bryans, J.S. et al. (Pfizer Inc.) *Bicyclic amino acids as pharmaceutical agents*. WO 0128978.

MRZ-2/705

304816

1-(1,3,3,5,5-Pentamethylcyclohexyl)pyrrolidine hydrochloride



C15 H29 N . HCl; Mol wt: 259.8620

ACTION – NMDA receptor antagonist, a representative compound from a series of 1-cyclic amino-alkylcyclohexane derivatives with excellent anticonvulsant and antiseizure activity. *In vitro*, compound exhibited a K_i value of 7.14 ± 1.7 μ M against [3 H]-MK-801 binding, as well as IC_{50} values of 25.40 ± 4.1 and 12.32 ± 1.19 μ M, respectively, against NMDA-induced currents in a patch-clamp assay and in a glutamate toxicity assay. *In vivo*, compound exhibited potent anticonvulsant effects against maximal electroshock-induced convulsions (ED_{50} = 9.55 mg/kg i.p.), exhibiting a therapeutic index relative to inhibition of traction reflex impairment or rotarod failure of 3.9 and 5.4, respectively; it was also active in the amygdala kindling model in rats at 10 and 20 mg/kg i.p.

SOURCE – Merz.

REFERENCES

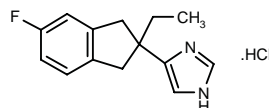
1. Gold, M. et al. (Merz & Co. GmbH) *1-Cyclic amino-alkylcyclohexane cpds., pharmaceutical compsns. thereof, and their use as anticonvulsants*. WO 0132640.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

JP-1730*

202370

4-(2-Ethyl-5-fluoroindan-2-yl)-1H-imidazole hydrochloride



C14 H15 F N2 . HCl; Mol wt: 266.7454

ACTION – Selective α_2 -adrenoceptor antagonist with high affinity for all human α_2 -adrenoceptor subtypes (K_i = 9.2, 17 and 55 nM, respectively, for α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors) and low affinity at rat brain α_1 -adrenoceptors and rat liver imidazoline I_2 binding sites (K_i > 3000 nM). Compound exhibited functional antagonism at α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors (K_b = 8.4, 16 and 4.7 nM, respectively). *In vivo* in the MPTP-lesioned marmoset model of Parkinson's disease, compound reduced L-DOPA-induced dyskinesia in a dose-dependent manner (1-10 mg/kg p.o.), with a significant 40% reduction at 10 mg/kg. Potentially useful for the management of dyskinesia and related movement disorders in Parkinson's disease.

SOURCES – Juvantia; Orion Corporation.

REFERENCES

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2. Engström, M. et al. *JP-1730, a novel antagonist of α_2 -adrenoceptors for the treatment of dyskinesia in Parkinson's disease*. Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-MO-010.

3. Honkanen, A. et al. *JP 1730, a novel α_2 -adrenoceptor antagonist, enhances apomorphine and L-dopa-induced circling behavior in the rat*. Soc Neurosci Abst 1999, 25(Part 2): Abst 541.20.

4. Merivuori, H. et al. *JP-1730, a selective α_2 -adrenergic receptor antagonist, reduces L-DOPA-induced dyskinesia in the MPTP-lesioned primate*. Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-TU-210.

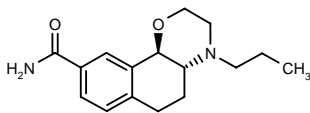
5. Savola, J.-M. et al. *JP-1730, a novel antagonist of α_2 -adrenoceptors, has potential as a new treatment for Parkinson's disease*. Mov Disord 2000, 15(Suppl. 3): Abst P247.

6. *Company Profile: Juvantia*. DailyDrugNews.com (Daily Essentials) 1999, Dec 8.

*Identified compound **202370** (see **MPV-1743AIII**) Drug Data Rep 1994, 016(01): 0032.

S-32504***273930**

(+)-(4a*R*,10b*R*)-4-Propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-9-carboxamide



C16 H22 N2 O2; Mol wt: 274.3618

ACTION – Dopamine D3 receptor agonist with 40-fold selectivity over D2 receptors ($pK_i = 8.06$ and 6.45 , respectively; $pEC_{50} = 8.6$ and 6.2 , respectively). *In vivo*, it was more active than ropinirole in models predictive of antiparkinsonian activity in rats and marmosets, and more active than fluoxetine in experiments indicative of antidepressant activity such as the forced swimming test in mice and chronic mild stress in rats. Potentially useful for the treatment of Parkinson's disease and depression.

SOURCE – Servier.

REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) *Disubst. trans-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b]-1,4-oxazines, process for their preparation and pharmaceutical compns. containing them.* CA 2246482, EP 0899267, FR 2767825, JP 1999130759, US 6025356.

2. Millan, M.J. et al. *S-32504, a novel and potent naphthoxazine agonist at dopamine D3 receptors.* Soc Neurosci Abstr 1999, 25(Part 2): Abstr 588.2.

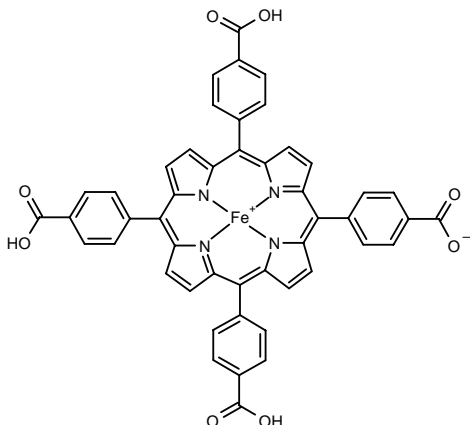
3. Peglion, J.-L. et al. *Discovery of S32504. A preferential agonist at dopamine D3 vs. D2 receptors possessing antiparkinsonian and antidepressant properties.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abstr MEDI 208.

*Identified compound **273930** Drug Data Rep 1999, 021(05): 0393.

TREATMENT OF NEURODEGENERATIVE DISEASES

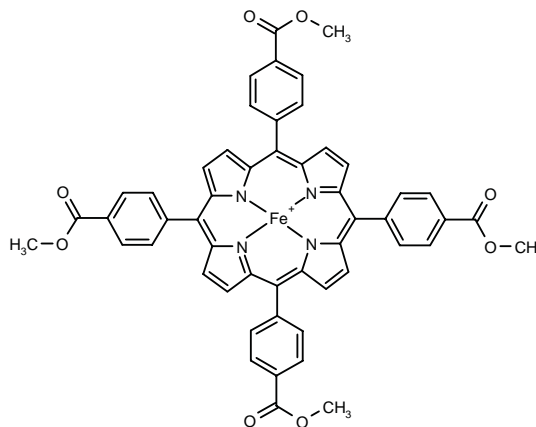
303768

[5,10,15,20-Tetrakis(4-carboxyphenyl)-21*H*,23*H*-porphyrin]iron



C48 H27 Fe N4 O8; Mol wt: 843.6063

ACTION – A representative compound from a series of metalloporphyrins with antioxidant properties, useful for the treatment of neurodegenerative disorders involving motor neuron death such as amyotrophic lateral sclerosis (ALS), spinal cord injury, traumatic spinal cord injury, Parkinson's disease and neurodegenerative diseases due to neurotoxins such as MPTP or due to oxidative injury, and which may further be used as a preservation solution for donor organs. *In vitro*, compound was shown to concentration-dependently decompose peroxynitrite. In addition, it was shown to concentration-dependently protect primary cultures of rat motor neurons from growth factor withdrawal (conditions known to cause peroxynitrite-mediated apoptotic cell death) for 24 and 72 h; long-term protection (> 16 days) was also observed in another experiment at 0.1 and 1.0 μ M, being more effective than brain-derived neurotrophic factor (BDNF). When it was tested in ALS-SOD1 (G93A) transgenic mice at 1 mg/kg/day i.p., it was shown to significantly prolong survival of animals even if treatment was initiated after onset of the disease. Furthermore, compound is reported to protect isolated hearts from ischemia–reperfusion injury. Another specifically claimed porphyrin is:



303769: C52 H36 Fe N4 O8

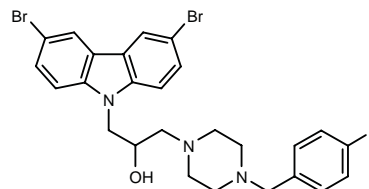
SOURCE – UAB Research Foundation, Birmingham, AL (US).

REFERENCES

1. Crow, J.P. and Estévez, A.G. (UAB Research Foundation) *Metalloporphyrin treatment of neurologic disease.* WO 0126655.

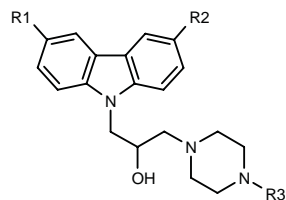
304120

(±)-1-(3,6-Dibromo-9*H*-carbazol-9-yl)-3-[4-(4-fluorobenz-yl)piperazin-1-yl]propan-2-ol



C26 H26 Br2 F N3 O; Mol wt: 575.3174

ACTION – Inhibitor of the cellular death agonist Bax that also blocks the release of cytochrome *c*. In *in vitro* assays, this compound inhibited the mitochondrial cytochrome *c* release triggered by Bid-induced Bax activation (–68%) or by Bax activation (–51%) at 10 and 5 µM, respectively. It displayed a neuronal survival rate of 45% at 10 µM. Potentially useful for the treatment of apoptosis-related diseases including neurodegenerative and autoimmune diseases, ischemia and infertility. Other exemplified 9-(piperazinyllalkyl)carbazoles are:



Compound	R1	R2	R3	Formula
304121	Ph	H	H	C ₂₈ H ₂₇ N ₃ O
304122	Br	Br	3-thienyl-CH2	C ₂₄ H ₂₅ Br ₂ N ₃ OS

SOURCE – Applied Research Systems.

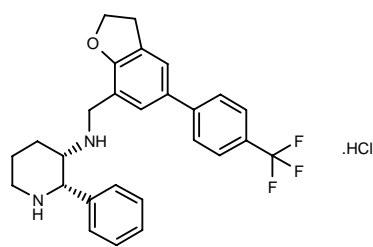
REFERENCES

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TREATMENT OF NAUSEA AND VOMITING

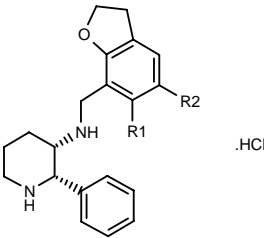
303711

2(S)-Phenyl-*N*-[5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-benzofuran-7-ylmethyl]piperidin-3(S)-amine hydrochloride



C27 H27 F3 N2 O . HCl; Mol wt: 488.9782

ACTION – Substance P antagonist (*K_i* = 1.01 nM against [³H]-substance P binding to human NK₁ receptors cloned in CHO cells) shown to inhibit cisplatin-induced retching and vomiting in ferrets by 88.4 and 91.1%, respectively, at 0.3 mg/kg i.v. Potentially useful for the treatment of respiratory, CNS, gastrointestinal, circulatory and inflammatory disorders and pain. Within this series of piperidine derivatives, the following are also included:



Compound	R1	R2	Formula
303712	H	1-tetrazolyl	C ₂₁ H ₂₄ N ₆ O.HCl
303713	H	Ph	C ₂₆ H ₂₈ N ₂ O.HCl
303714	H	5-CF3-1,2,4-oxadiazol-3-yl	C ₂₃ H ₂₃ F ₃ N ₄ O ₂ .HCl
303715		-CH2CH2O-	C ₂₂ H ₂₆ N ₂ O ₂ .HCl

SOURCE – Hisamitsu.

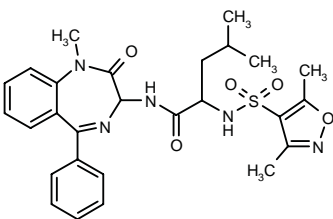
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TREATMENT OF COGNITION DISORDERS

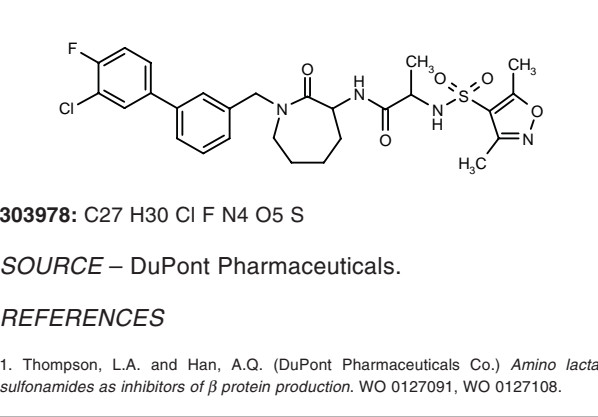
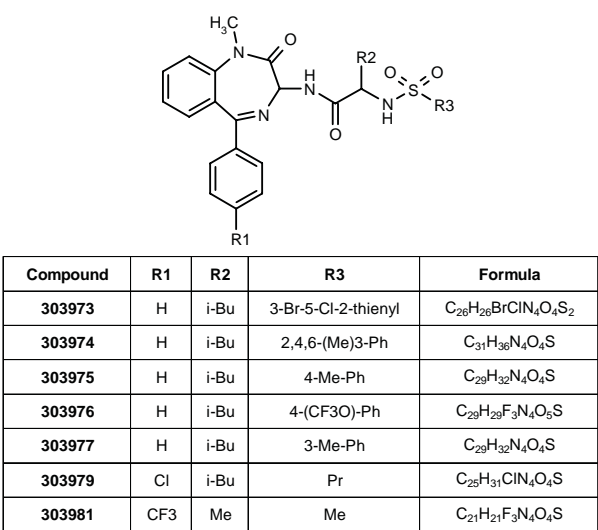
303972

2-(3,5-Dimethylisoxazol-4-ylsulfonamido)-4-methyl-*N*-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl)pentanamide



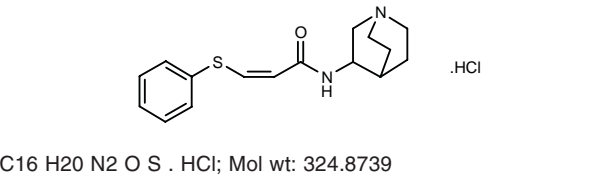
C27 H31 N5 O5 S; Mol wt: 537.6379

ACTION – Antiamyloidogenic agent that inhibits the production of β-amyloid peptide through inhibition of γ-secretase. This compound is expected to be useful for the treatment of neurological disorders related to β-amyloid production such as Alzheimer’s disease and Down’s syndrome. Other specifically claimed amino lactam sulfonamides include the following:

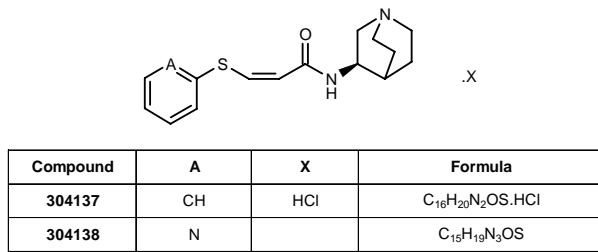


304136

3-(Phenylsulfanyl)-N-(3-quinuclidinyl)-2(Z)-propenamide hydrochloride



ACTION – A selective α7 nicotinic acetylcholine receptor (nAChR) agonist with potential in the treatment or prevention of cognitive disorders such as Alzheimer’s disease, attention deficit hyperactivity disorder and memory loss, and psychotic disorders such as schizophrenia, mania and anxiety. Compound may also be useful as an analgesic, as well as in the treatment or prevention of Parkinson’s disease, Huntington’s disease, Tourette’s syndrome, jet lag and in smoking cessation. Other specifically claimed compounds from this series of quinuclidine acrylamides include the following:



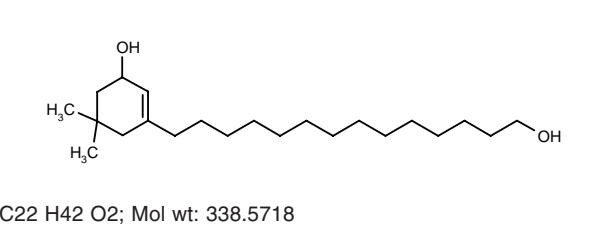
SOURCE – AstraZeneca.

REFERENCES

1. Schmiesing, R. (AstraZeneca AB) *Quinuclidine acrylamides*. WO 0129034.

304341

3-(14-Hydroxytetradecyl)-5,5-dimethyl-2-cyclohexen-1-ol



ACTION – Agent for the treatment or prevention of neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, Huntington’s chorea, Pick’s disease, spinocerebellar degeneration and amyotrophic lateral sclerosis by virtue of its ability to stimulate nerve cell proliferation and neurite growth, as demonstrated at 1 μM in cultures of fetal rat brain neurons. A representative compound from a series of cyclohexenol derivatives.

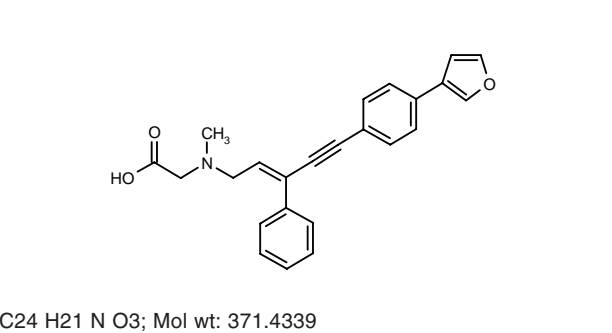
SOURCE – Meiji Milk Products.

REFERENCES

1. Ban, R. et al. (Meiji Milk Products Co., Ltd.) *Cyclohexenole derivs. and medicines containing them*. JP 2001089404.

304700

2-[N-[5-[4-(3-Furyl)phenyl]-3-phenyl-2-penten-4-ynyl]-N-methylamino]acetic acid



ACTION – A representative compound from a series of diaryl-ynes that inhibits glycine transport or reuptake via the GlyT-1 transporter. Potentially useful for the treatment of schizophrenia and cognition disorders, particularly Alzheimer’s disease.

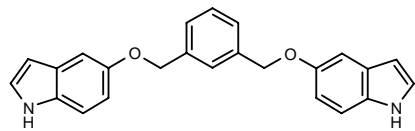
SOURCE – NPS Allelix.

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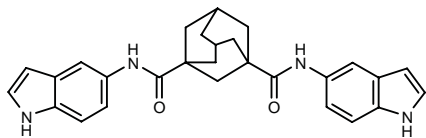
304717

1,3-Bis(1*H*-indol-5-yl-oxymethyl)benzene



C24 H20 N2 O2; Mol wt: 368.4340

ACTION – Positive modulator of nicotinic receptor agonists that enhances the efficacy of agonists at nicotinic receptors and may thus be used for the treatment of conditions associated with reductions in nicotinic transmission such as schizophrenia, mania and manic depression, anxiety, Alzheimer’s disease, learning, cognition and attention deficits, memory loss, Lewy body dementia, attention deficit hyperactivity disorder, Parkinson’s disease, Huntington’s disease, Tourette’s syndrome, jet lag, nicotine addiction, pain and ulcerative colitis. Another specifically claimed compound from this series of substituted indole derivatives is:



304719: C28 H28 N4 O2

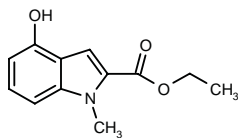
SOURCE – AstraZeneca.

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1. Balestra, M. et al. (AstraZeneca AB) *Positive modulators of nicotinic receptor agonists*. WO 0132620.

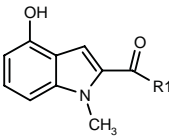
304720

4-Hydroxy-1-methyl-1*H*-indole-2-carboxylic acid ethyl ester



C12 H13 N O3; Mol wt: 219.2387

ACTION – Positive modulator of nicotinic receptor agonists that enhances the efficacy of agonists at nicotinic receptors and may thus be used for the treatment of conditions associated with reductions in nicotinic transmission such as schizophrenia, mania and manic depression, anxiety, Alzheimer’s disease, learning, cognition and attention deficits, memory loss, Lewy body dementia, attention deficit hyperactivity disorder, Parkinson’s disease, Huntington’s disease, Tourette’s syndrome, jet lag, nicotine addiction, pain and ulcerative colitis. Other specifically claimed compounds from this series of substituted indole derivatives include the following:



Compound	R1	Formula
304721	N(Me)CH2H2Ph	C ₁₉ H ₂₀ N ₂ O ₂
304722	NHCH2Ph	C ₁₇ H ₁₆ N ₂ O ₂
304723	NH(CH2)3Ph	C ₁₉ H ₂₀ N ₂ O ₂
304724	4-Cl-PhNH	C ₁₆ H ₁₃ ClN ₂ O ₂
304725	NHEt	C ₁₂ H ₁₄ N ₂ O ₂
304726	NHCH(CH2F)CH2Ph	C ₁₉ H ₁₉ FN ₂ O ₂
304727	(S)-NHCH(CH2N3)CH2Ph	C ₁₉ H ₁₉ N ₅ O ₂
304728	(R)-NHCH2CH(F)CH2Ph	C ₁₉ H ₁₉ FN ₂ O ₂

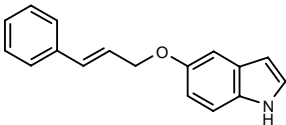
SOURCE – AstraZeneca.

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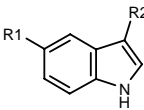
304729

5-(3-Phenyl-2-propenyloxy)-1*H*-indole



C17 H15 N O; Mol wt: 249.3115

ACTION – Positive modulator of nicotinic receptor agonists that enhances the efficacy of agonists at nicotinic receptors and may thus be used for the treatment of conditions associated with reductions in nicotinic transmission such as schizophrenia, mania and manic depression, anxiety, Alzheimer’s disease, learning, cognition and attention deficits, memory loss, Lewy body dementia, attention deficit hyperactivity disorder, Parkinson’s disease, Huntington’s disease, Tourette’s syndrome, jet lag, nicotine addiction, pain and ulcerative colitis. Other specifically claimed compounds from this series of substituted indole derivatives are:



Compound	R1	R2	Formula
304730	OCH2Ph	CH2CN	C ₁₇ H ₁₄ N ₂ O
304731	OCH2CH2OPh	H	C ₁₆ H ₁₅ NO ₂
304732	2-Naph-CH2O	H	C ₁₉ H ₁₅ NO
304733	CH2CONHPh	H	C ₁₆ H ₁₄ N ₂ O
304734	2-furyl-CH2NHCSNH	H	C ₁₄ H ₁₃ N ₃ OS

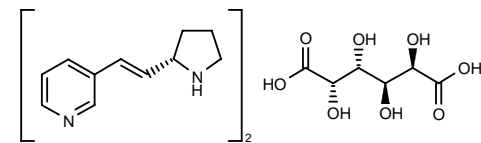
SOURCE – AstraZeneca.

REFERENCES

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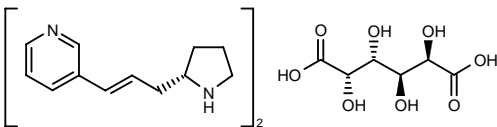
304887

3-[(*E*)-2-[2(*S*)-Pyrrolidinyl]vinyl]pyridine hemigalactarate



2(C11 H14 N2).C6 H10 O8; Mol wt: 558.6282

ACTION – Agent for the treatment of CNS disorders and pain, a nicotinic acetylcholine receptor agonist (K_i = 306 nM) proven to promote neurotransmitter release from rat brain synaptosomes with an E_{max} value of 48%, while exhibiting only weak or negligible activation of muscle-type and ganglion-type nicotinic acetylcholine receptors. Another specifically claimed compound from this series of aryl olefinic azacyclic and aryl acetylenic azacyclic derivatives is:



304888: 2(C12 H16 N2). C6 H10 O8

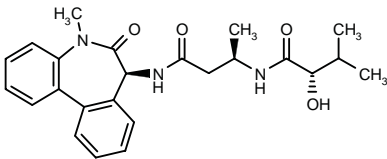
SOURCE – Targacept.

REFERENCES

1. Schmitt, J.D. et al. (Targacept, Inc.) *Aryl olefinic azacyclic, and aryl acetylenic azacyclic cpds., pharmaceutical compsns. containing them and their use as inhibitors of nicotinic cholinergic receptors.* WO 0132264.

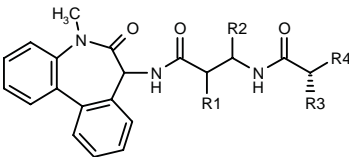
305006

2(*S*)-Hydroxy-3-methyl-*N*-[1(*R*)-methyl-2-[*N*-[5-methyl-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7(*S*)-yl]-carbamoyl]ethyl]butyramide



C24 H29 N3 O4; Mol wt: 423.5101

ACTION – Inhibitor of the release and/or the production of β -amyloid peptide that is expected to be useful for the treatment of Alzheimer's disease, as well as for preventing the onset of this disease in patients at risk of developing it. Other specifically claimed β -amino acid compounds are:



Compound	R1	R2	R3	R4	Isomer	Formula
305007	H	(S)-Me	OH	i-Pr	7S	C ₂₄ H ₂₉ N ₃ O ₄
305009	H	(S)-Me	OH	3,5-(F)2-Ph	7S	C ₂₇ H ₂₅ F ₂ N ₃ O ₄
305010	H	(R)-Me	OH	3,5-(F)2-Ph	7S	C ₂₇ H ₂₅ F ₂ N ₃ O ₄
305012	(R)-Me	H	OH	i-Pr	7S	C ₂₄ H ₂₉ N ₃ O ₄
305013	(S)-Me	H	OH	i-Pr	7S	C ₂₄ H ₂₉ N ₃ O ₄
305015	(R)-Me	H	OH	3,5-(F)2-Ph	7S	C ₂₇ H ₂₅ F ₂ N ₃ O ₄
305017	(S)-Me	H	OH	3,5-(F)2-Ph	7S	C ₂₇ H ₂₅ F ₂ N ₃ O ₄
305020	H	H	H	3,5-(F)2-Ph		C ₂₆ H ₂₃ F ₂ N ₃ O ₃
305022	H	H	H	2-thienyl		C ₂₄ H ₂₃ N ₃ O ₃ S
305024	H	H	H	i-Pr		C ₂₃ H ₂₇ N ₃ O ₃
305026	H	H	H	Ph		C ₂₆ H ₂₅ N ₃ O ₃

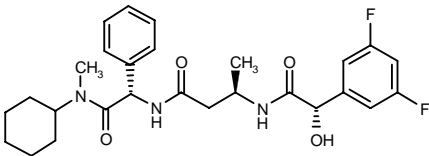
SOURCE – Lilly.

REFERENCES

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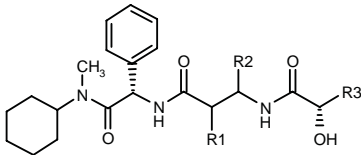
305030

N-[1(*S*)-(N-Cyclohexyl-N-methylcarbamoyl)-1-phenylmethyl]-3(*R*)-[2(*S*)-(3,5-difluorophenyl)-2-hydroxy-acetamido]butyramide



C27 H33 F2 N3 O4; Mol wt: 501.5707

ACTION – Inhibitor of the release and/or the production of β -amyloid peptide that is expected to be useful for the treatment of Alzheimer's disease, as well as for preventing the onset of this disease in patients at risk of developing it. Other specifically claimed β -amino acid compounds are:



Compound	R1	R2	R3	Formula
305031	H	(S)-Me	3,5-(F)2-Ph	C ₂₇ H ₃₃ F ₂ N ₃ O ₄
305032	H	(R)-Me	i-Pr	C ₂₄ H ₃₇ N ₃ O ₄
305033	H	(S)-Me	i-Pr	C ₂₄ H ₃₇ N ₃ O ₄
305034	Me	H	3,5-(F)2-Ph	C ₂₇ H ₃₃ F ₂ N ₃ O ₄
305036	(R)-Me	H	i-Pr	C ₂₄ H ₃₇ N ₃ O ₄
305037	(S)-Me	H	i-Pr	C ₂₄ H ₃₇ N ₃ O ₄

SOURCE – Lilly.

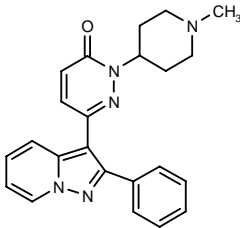
REFERENCES

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FR-194921*

261545

2-(1-Methylpiperidin-4-yl)-6-(2-phenylpyrazolo[1,5-a]pyridin-3-yl)pyridazin-3(2*H*)-one



C23 H23 N5 O; Mol wt: 385.4687

ACTION – Potent and selective adenosine A₁ receptor antagonist (K_i = 6.6 and 5400 nM for A₁ and A_{2A} receptors, respectively) with high oral bioavailability (60.6%) and good blood–brain barrier permeability in rats (brain/plasma ratio = 1.39) following an oral dose of 32 mg/kg. A candidate for further pharmacological evaluation as a cognition enhancer or antidepressant.

SOURCE – Fujisawa.

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1. Akahane, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Pyrazolopyridine cpd. and pharmaceutical use thereof*. EP 0925299, JP 2000514821, US 6124456, WO 9803507.

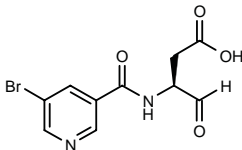
2. Kuroda, S. et al. *Design, synthesis and biological evaluation of a novel series of potent, orally active adenosine A₁ receptor antagonists with high blood-brain barrier permeability*. Chem Pharm Bull 2001, 49(8): 988.

*Identified compound **261545** Drug Data Rep 1998, 020(05): 0389.

**TREATMENT OF
CEREBROVASCULAR DISEASES**

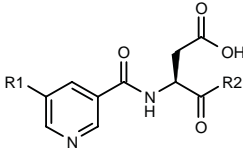
303920

3(*S*)-(5-Bromopyridin-3-ylcarboxamido)-4-oxobutyric acid



C10 H9 Br N2 O4; Mol wt: 301.0951

ACTION – Caspase 3 inhibitor, potentially useful for the treatment of cardiac and cerebral ischemia/reperfusion injury, type 1 diabetes, AIDS, cerebral and spinal cord trauma, organ damage during transplantation, alopecia, aging, Parkinson’s disease, Alzheimer’s disease, Down’s syndrome, spinal muscular atrophy, multiple sclerosis and neurodegenerative disorders. Other specifically claimed compounds from this series of nicotinyl aspartyl ketones include the following:



Compound	R1	R2	Formula
303921	4-CO2H-Ph	H	C ₁₇ H ₁₄ N ₂ O ₆
303922	CONHCH2Ph	4-F-PhCH2SCH2	C ₂₆ H ₂₄ FN ₃ O ₅ S
303925	CON(i-Pr) ₂	4-F-PhCH2SCH2	C ₂₅ H ₃₀ FN ₃ O ₅ S
303927	1-Pip-CO	4-F-PhCH2SCH2	C ₂₄ H ₂₆ FN ₃ O ₅ S
303928	CONHCH2CH2CO2Et	4-F-PhCH2SCH2	C ₂₄ H ₂₆ FN ₃ O ₇ S
303929	SO2N(Et) ₂	4-F-PhCH2SCH2	C ₂₂ H ₂₆ FN ₃ O ₆ S ₂
303930	cyclopropyl-NHSO2	CH2OPh	C ₂₀ H ₂₁ N ₃ O ₇ S
303931	Br	(CH2)3Ph	C ₁₉ H ₁₉ BrN ₂ O ₄
303932	cyclopropyl-NHSO2	1-pyrrolidinyl-CH2	C ₁₈ H ₂₄ N ₄ O ₆ S

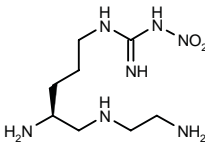
SOURCE – Merck Frosst.

REFERENCES

1. Black, C. et al. (Merck Frosst Canada Inc.) *Nicotinyl aspartyl ketones as inhibitors of caspase-3*. WO 0127085.

305859

N-[4(*S*)-Amino-5-(2-aminoethylamino)pentyl]-*N*’-nitro-guanidine



C8 H21 N7 O2; Mol wt: 247.3009

ACTION – Potent inhibitor of neuronal nitric oxide synthase (nNOS; K_i = 120 nM) with high selectivity over inducible and endothelial isoforms (K_i = 39 and 314 μM, respectively). Potentially useful for the treatment of stroke.

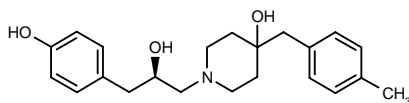
SOURCES – Northwestern University, Evanston, IL (US); University of Texas System, Austin, TX (US).

REFERENCES

1. Hah, J.-M. et al. *Reduced amide bond peptidomimetics. (4S)-N-(4-Amino-5-[aminoalkyl]aminopentyl)-N’-nitroguanidines, potent and highly selective inhibitors of neuronal nitric oxide synthase*. J Med Chem 2001, 44(16): 2667.

307048

(-)-1-[2(*R*)-Hydroxy-3-(4-hydroxyphenyl)propyl]-4-(4-methylbenzyl)piperidin-4-ol



C₂₂ H₂₉ N O₃; Mol wt: 355.4751

ACTION – NR1/2B subtype-selective NMDA receptor antagonist with an IC₅₀ value of 19 nM in a functional assay in *Xenopus* oocytes expressing recombinant rat NR1/2B receptors, and > 500-fold selectivity over the NR1/2A subtype. Compound showed 1490-fold binding selectivity for NMDA receptors over α₁-adrenoceptors (K_i = 4.9 and 7300 nM, respectively). *In vivo*, it protected mice from audiogenic seizures with an ED₅₀ value of 10 mg/kg i.p. Potentially useful for the treatment of neurodegenerative diseases such as stroke, brain trauma, pain and Parkinson's disease.

SOURCE – Roche.

REFERENCES

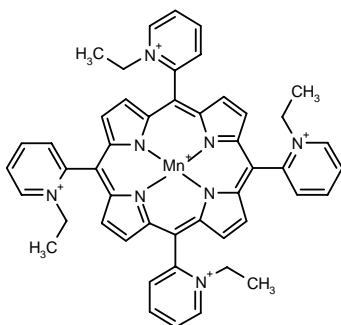
1. Alanine, A. et al. (F. Hoffmann-La Roche AG) 4-Hydroxy-piperidine derivs. EP 0824098, JP 1998067742.
2. Pinard, E. et al. Discovery of (*R*)-1-[2-hydroxy-3-(4-hydroxy-phenyl)-propyl]-4-(4-methyl-benzyl)-piperidin-4-ol: A novel NR1/2B subtype selective NMDA receptor antagonist. Bioorg Med Chem Lett 2001, 11(16): 2173.

AEOL-10113

293454

(*SP-4-1*)-[[2,2',2'',2'''-(21*H*,23*H*-Porphine-5,10,15,20-tetrayl-κ*N*²¹,κ*N*²²,κ*N*²³,κ*N*²⁴)tetrakis[1-ethylpyridiniumato]](2-)]manganese(5+)

MnTE-2-PyP⁵⁺



C₄₈ H₄₄ Mn N₈; Mol wt: 787.8696

ACTION – Metalloporphyrin catalytic antioxidant that protects rat brain cortical cultures from death induced by serum and glucose/oxygen deprivation and exerts neuroprotective activity when administered up to 6 h after ischemia in experimental models. Compound (300 ng) given i.c.v. to rats 60 min before ischemia improved neurological scores and reduced total infarct size by 70%; when it was given 5 or 90 min after reperfusion; it induced a 70-77% reduction in total infarct volume, but no protection was seen when it was administered 12 h after reperfusion. Compound showed promising activity in several other preclinical models including a mouse model of human juvenile-onset diabetes, where it prevented diabetes in 50% of the mice and significantly delayed disease onset in the remaining mice, a rat model of radiation-induced toxicity, where it produced significant protection of normal lung tissue, and a rat model of breast cancer, where it enhanced the antitumor effect of radiation. Potential clinical candidate for the treatment of stroke.

SOURCES – Duke University, Durham, NC (US); Incara.

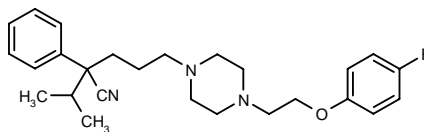
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1. Fridovich, I. and Batinic-Haberle, I. (Duke University) Substd. porphyrins. EP 1045851, WO 9923097.
2. Bloodworth, A. et al. Manganese-porphyrin reactions with lipid and lipoproteins. Free Radical Biol Med 2000, 28(7): 1017.
3. Mackensen, G.B. et al. Neuroprotection from delayed postischemic administration of a metalloporphyrin catalytic antioxidant. J Neurosci 2001, 21(13): 4582.
4. Patel, M.N. et al. A metalloporphyrin catalytic antioxidant protects against ischemic brain damage with a six-hour therapeutic window. Soc Neurosci Abst 2000, 26(Part 1): Abst 289.7.
5. Sheng, H. et al. Postischemic IV administration of MnTE-2PyP, a metalloporphyrin catalytic antioxidant, reduces histologic/neurologic damage after murine MCAO. Soc Neurosci Abst 2000, 26(Part 1): Abst 289.6.
6. Small-molecule antioxidant patent granted. DailyDrugNews.com (Daily Essentials) 2000, Sept 12.

E-2050

295854

(-)-5-[4-[2-(4-Fluorophenoxy)ethyl]piperazin-1-yl]-2-isopropyl-2-phenylpentanenitrile



C₂₆ H₃₄ F N₃ O; Mol wt: 423.5726

ACTION – Neuron-selective calcium channel blocker (IC₅₀ = 3.3 μM in voltage-clamp assays) proven to inhibit glutamate release from brain slices with an IC₅₀ value of 2.9 μM and to protect mice from audiogenic seizures (ED₅₀ = 10 mg/kg i.v.). In a transient middle cerebral artery (MCA) occlusion model in rats, compound at doses of 5 and 15 mg/kg/h dose-dependently reduced cortical infarct volume by 37 and 54%, respectively, and a dose of 20 mg/kg given 2 h before permanent MCA occlusion gave a 30% reduction in cortical infarct volume. Potentially useful for the treatment of stroke.

SOURCE – Eisai.

REFERENCES

1. Yamamoto, N. et al. (Eisai Co., Ltd.) *N,N*-Substd. cyclic amine derivs. EP 1099692, JP 2000169462, WO 0005210.

2. Wang, Z. et al. *Solubility of E2050 at various pH: A case where solubility is affected by the amount of solid*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3043.

3. Yamamoto, N. et al. *Discovery of a potent neuron-selective calcium channel blocker: Structure-activity relationships and neuroprotective effects of novel piperazine derivatives*. 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 1P-22.

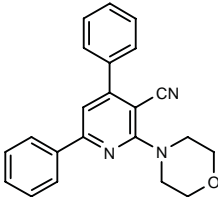
4. Yamamoto, N. et al. *Discovery of a potent neuron-selective calcium channel blocker: Structure-activity relationships and neuroprotective effects of novel piperazine derivatives*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 51.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

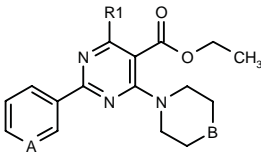
304890

2-(4-Morpholinyl)-4,6-diphenylpyridine-3-carbonitrile



C22 H19 N3 O; Mol wt: 341.4121

ACTION – Agent for the treatment of allergy, autoimmune diseases, rheumatism and arteriosclerosis with CD40 function-inhibitory activity. *In vitro*, compound was shown to inhibit the mixed lymphocyte reaction (MLR) in human peripheral blood lymphocytes (96% inhibition at 5 μM), as well as IL-12 production induced by human interferon gamma, DMSO and anti-CD40 antibody in human monocytic THP-1 cells (86% inhibition at 25 μM). In addition, it is reported to inhibit anti-CD40 antibody-induced agglutination of Ramos cells and IgE production induced by anti-CD40 antibody and IL-4 in human peripheral blood lymphocytes. Other compounds include the following:



Compound	R1	A	B	Formula
304891	Ph	CH	O	C ₂₃ H ₂₃ N ₃ O ₃
304892	NHPh	N	S	C ₂₂ H ₂₃ N ₃ O ₂ S

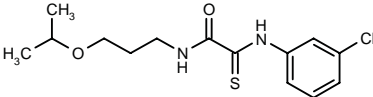
SOURCE – Sankyo.

REFERENCES

1. Saito, S. et al. (Sankyo Co., Ltd.) *Pyrimidine derivs*. JP 2001089452.

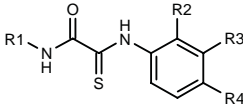
304936

2-(3-Chlorophenylamino)-N-(3-isopropoxypropyl)-2-thioacetamide



C14 H19 Cl N2 O2 S; Mol wt: 314.8351

ACTION – An inhibitor of CD45 tyrosine dephosphorylase, as demonstrated using human leukemia Ball-1 cell membranes (IC₅₀ = 0.10 μM). Potentially useful for the treatment of allergic disorders. Other exemplified *N*-aryl thiooxamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
304937	(E)-4-(4-MeO-Ph)-CH=CHPh	-CH=CHCH=CH-	H	H	C ₂₇ H ₂₂ N ₂ O ₂ S
304938	(CH ₂) ₃ OMe	H	H	Et	C ₁₄ H ₂₀ N ₂ O ₂ S
304939	1-adamantyl-CH ₂	H	H	Cl	C ₁₉ H ₂₃ ClN ₂ OS
304940	1-adamantyl-CH ₂	H	H	OMe	C ₂₀ H ₂₆ N ₂ O ₂ S
304941	1-adamantyl-CH ₂	-CH=CHCH=CH-	H	H	C ₂₃ H ₂₆ N ₂ OS
304942	4,6-(MeO)2-2-pyrimidinyl	H	Cl	H	C ₁₄ H ₁₃ ClN ₄ O ₃ S
304943	4,6-(MeO)2-2-pyrimidinyl	H	H	Cl	C ₁₄ H ₁₃ ClN ₄ O ₃ S
304944	4,6-(MeO)2-2-pyrimidinyl	H	H	Et	C ₁₆ H ₁₈ N ₄ O ₃ S
304945	4-Me-5-(CO ₂ Et)-2-thiazolyl	H	Cl	H	C ₁₅ H ₁₄ ClN ₃ O ₃ S ₂

SOURCE – Taisho.

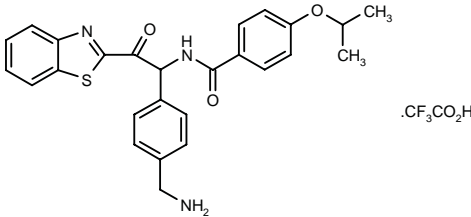
REFERENCES

1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *N-Arylthiooxamide derivs*. JP 2001114753.

ASTHMA THERAPY

303872

N-[1-[4-(Aminomethyl)phenyl]-2-(2-benzothiazolyl)-2-oxoethyl]-4-isopropoxybenzamide trifluoroacetate



C26 H25 N3 O3 S . C2 H F3 O2; Mol wt: 573.5894

SOURCE – Eisai.

REFERENCES

1. Yamamoto, N. et al. (Eisai Co., Ltd.) *N,N*-Substd. cyclic amine derivs. EP 1099692, JP 2000169462, WO 0005210.

2. Wang, Z. et al. *Solubility of E2050 at various pH: A case where solubility is affected by the amount of solid.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3043.

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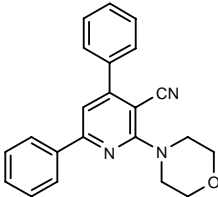
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RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

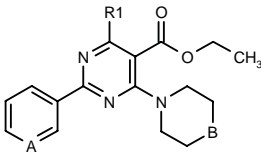
304890

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Compound	R1	A	B	Formula
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304892	NHPh	N	S	C ₂₂ H ₂₃ N ₃ O ₂ S

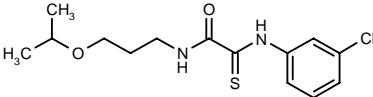
SOURCE – Sankyo.

REFERENCES

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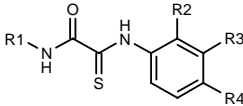
304936

2-(3-Chlorophenylamino)-N-(3-isopropoxypropyl)-2-thioacetamide



C14 H19 Cl N2 O2 S; Mol wt: 314.8351

ACTION – An inhibitor of CD45 tyrosine dephosphorylase, as demonstrated using human leukemia Ball-1 cell membranes (IC₅₀ = 0.10 μM). Potentially useful for the treatment of allergic disorders. Other exemplified *N*-aryl thiooxamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
304937	(E)-4-(4-MeO-Ph)-CH=CHPh	-CH=CHCH=CH-	H	H	C ₂₇ H ₂₂ N ₂ O ₂ S
304938	(CH ₂) ₃ OMe	H	H	Et	C ₁₄ H ₂₀ N ₂ O ₂ S
304939	1-adamantyl-CH ₂	H	H	Cl	C ₁₉ H ₂₃ ClN ₂ OS
304940	1-adamantyl-CH ₂	H	H	OMe	C ₂₀ H ₂₆ N ₂ O ₂ S
304941	1-adamantyl-CH ₂	-CH=CHCH=CH-	H	H	C ₂₃ H ₂₆ N ₂ OS
304942	4,6-(MeO)2-2-pyrimidinyl	H	Cl	H	C ₁₄ H ₁₃ ClN ₄ O ₃ S
304943	4,6-(MeO)2-2-pyrimidinyl	H	H	Cl	C ₁₄ H ₁₃ ClN ₄ O ₃ S
304944	4,6-(MeO)2-2-pyrimidinyl	H	H	Et	C ₁₆ H ₁₈ N ₄ O ₃ S
304945	4-Me-5-(CO ₂ Et)-2-thiazolyl	H	Cl	H	C ₁₅ H ₁₄ ClN ₃ O ₃ S ₂

SOURCE – Taisho.

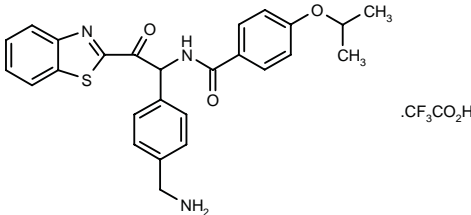
REFERENCES

1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *N-Arylthiooxamide derivs.* JP 2001114753.

ASTHMA THERAPY

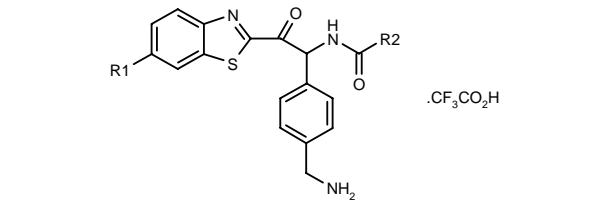
303872

N-[1-[4-(Aminomethyl)phenyl]-2-(2-benzothiazolyl)-2-oxo-ethyl]-4-isopropoxybenzamide trifluoroacetate

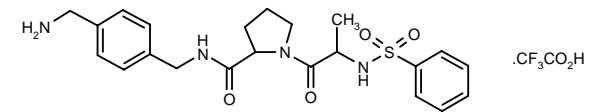


C26 H25 N3 O3 S . C2 H F3 O2; Mol wt: 573.5894

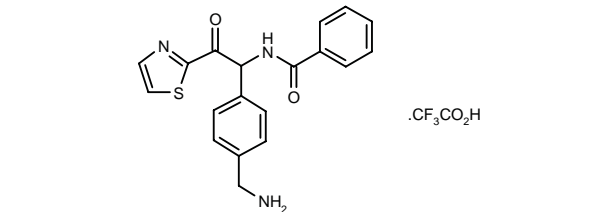
ACTION – Tryptase inhibitor, potentially useful in the treatment of inflammatory and other mast cell-mediated conditions, particularly asthma. Other exemplified compounds from this series of aminomethyl-(hetero)aryl derivatives include the following:



Compound	R1	R2	Formula
303873	H	2-Naph	C ₂₇ H ₂₁ N ₃ O ₂ S.C ₂ HF ₃ O ₂
303874	H	4-(MeSO ₂)-Ph	C ₂₄ H ₂₁ N ₃ O ₄ S ₂ .C ₂ HF ₃ O ₂
303875	H	4-i-Pr-Ph	C ₂₆ H ₂₅ N ₃ O ₂ S.C ₂ HF ₃ O ₂
303877	NHCOPh	Ph	C ₃₀ H ₂₄ N ₄ O ₃ S.C ₂ HF ₃ O ₂
303878	NHCOPh	Me	C ₂₅ H ₂₂ N ₄ O ₃ S.C ₂ HF ₃ O ₂
303879	NHSO ₂ CH ₂ Ph	Me	C ₂₅ H ₂₄ N ₄ O ₄ S ₂ .C ₂ HF ₃ O ₂



303876: C22 H28 N4 O4 S . C2 H F3 O2



303880: C19 H17 N3 O2 S . C2 H F3 O2

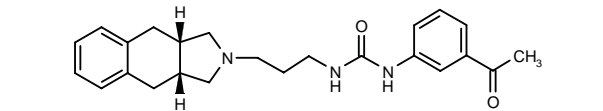
SOURCE – Protherics.

REFERENCES

1. Lively, S.E. et al. (Protherics plc) *Aminomethyl-(hetero)aryl derivs. and their use as tryptase inhibitors*. WO 0127096.

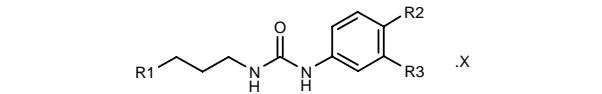
304237

cis-N-(3-Acetylphenyl)-N'-[3-(2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindol-2-yl)propyl]urea



C24 H29 N3 O2; Mol wt: 391.5121

ACTION – Chemokine CCR3 receptor modulator with potential for the treatment or prevention of a broad range of disorders including asthma, allergic disorders and inflammatory and autoimmune diseases. Other specifically claimed compounds from this series of bicyclic and tricyclic amines include the following:



Compound	R1	R2	R3	X	Formula
304238	trans-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindol-2-yl	H	Ac		C ₂₄ H ₂₉ N ₃ O ₂
304239	(±)-cis-6-F-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindol-2-yl	H	Ac		C ₂₄ H ₂₈ FN ₃ O ₂
304240	4-(4-F-PhCH ₂)-2-azabicyclo[2.2.2]oct-3-yl	F	H	HCl	C ₂₄ H ₂₉ F ₂ N ₃ O.HCl
304241	(1S,4R,6R)-6-(4-F-PhCH ₂)-2-azabicyclo[2.2.2]oct-2-yl	H	Ac	HCl	C ₂₆ H ₃₂ FN ₃ O ₂ .HCl
304242	(1R,4S,6S)-6-(4-F-PhCH ₂)-2-azabicyclo[2.2.2]oct-2-yl	F	H	HCl	C ₂₄ H ₂₉ F ₂ N ₃ O.HCl
304243	(1S,5R,6R)-6-(4-F-Ph)-3-azabicyclo[3.2.0]hept-3-yl	F	H		C ₂₂ H ₂₅ F ₂ N ₃ O
304244	(1S,5R,6R)-6-(4-F-Ph)-3-azabicyclo[3.2.0]hept-3-yl	H	Ac		C ₂₄ H ₂₈ FN ₃ O ₂

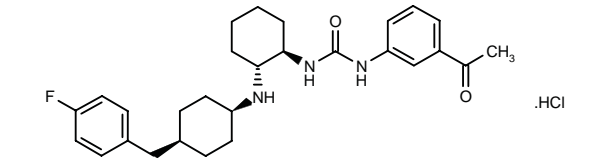
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Wacker, D.A. and Duncia, J.V. (DuPont Pharmaceuticals Co.) *Bicyclic and tricyclic amines as modulators of chemokine receptor activity*. WO 0129000.

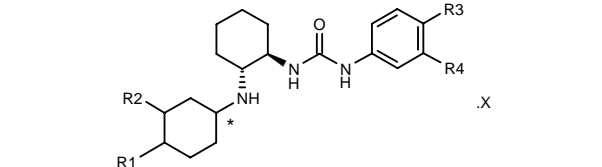
304245

N-(3-Acetylphenyl)-N'-[(1R,2R)-2-[cis-4-(4-fluorobenzyl)-cyclohexylamino]cyclohexyl]urea hydrochloride

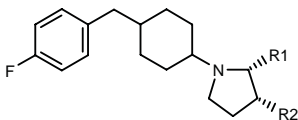


C28 H36 F N3 O2 . HCl; Mol wt: 502.0703

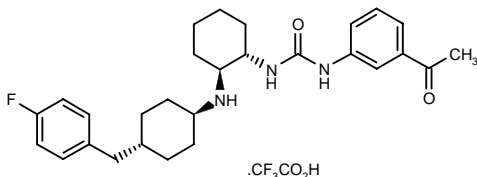
ACTION – Chemokine CCR3 receptor modulator with potential for the treatment or prevention of a broad range of disorders including asthma, allergic disorders and inflammatory and autoimmune diseases. Other specifically claimed compounds from this series of benzylcycloalkyl amines include the following:



Compound	R1	R2	R3	R4	*Isomer	X	Formula
304246	4-F-PhCH ₂	H	H	CN	cis	CF ₃ CO ₂ H	C ₂₇ H ₃₃ FN ₄ O.C ₂ HF ₃ O ₂
304248	H	4-F-PhCH ₂	H	Ac	1S,3R		C ₂₈ H ₃₆ FN ₃ O ₂
304249	H	4-F-PhCH ₂	F	H	1R,3R		C ₂₈ H ₃₃ F ₂ N ₃ O
304250	H	4-F-PhCH ₂	F	H	1S,3S		C ₂₈ H ₃₃ F ₂ N ₃ O



Compound	R1	R2	Formula
304251	3-Ac-PhNHCONHCH2	H	C ₂₇ H ₃₄ FN ₃ O ₂
304252	H	3-Ac-PhNHCONH	C ₂₆ H ₃₂ FN ₃ O ₂



304247: C28 H36 F N3 O2 . C2 H F3 O2

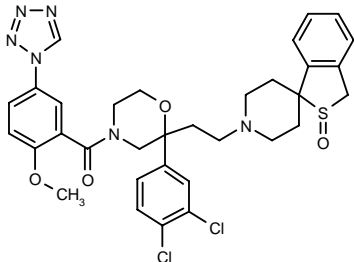
SOURCE – DuPont Pharmaceuticals.

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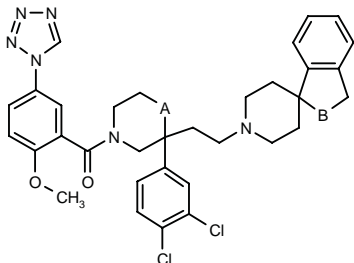
304312

1'-[2-[2-(3,4-Dichlorophenyl)-4-[2-methoxy-5-(1*H*-tetrazol-1-yl)benzoyl]morpholin-2-yl]ethyl]spiro[benzo[*c*]thiophen-1(3*H*),4'-piperidine] *S*-oxide



C33 H34 Cl2 N6 O4 S; Mol wt: 681.6416

ACTION – Tachykinin NK₁, NK₂ and NK₃ receptor antagonist reported to have good oral bioavailability, with potential for the treatment of chronic obstructive pulmonary disease, asthma, bronchitis, rhinitis, allergy, urinary incontinence and ulcerative colitis. Other exemplified compounds from this series of 2-alkoxybenzene derivatives include the following:



Compound	A	B	Formula
304313	-O-	-CH(OH)-	C ₃₄ H ₃₆ Cl ₂ N ₆ O ₄
304314	bond	-SO-	C ₃₃ H ₃₄ Cl ₂ N ₆ O ₃ S
304315	bond	-CH(OH)-	C ₃₄ H ₃₆ Cl ₂ N ₆ O ₃

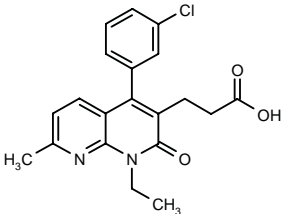
SOURCE – Sankyo.

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1. Nishi, T. et al. (Sankyo Co., Ltd.) *2-Alkoxybenzene derivs*. JP 2001187790, WO 0129027.

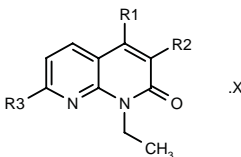
304502

3-[4-(3-Chlorophenyl)-1-ethyl-7-methyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]propionic acid



C20 H19 Cl N2 O3; Mol wt: 370.8341

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 11 nM or less against enzyme from rat ventricular muscle), reported to exhibit low hepatic metabolism in cultured rat and human hepatic microsomes and to display good oral absorption and duration of action following administration of 3 mg/kg p.o. to rats. Potentially useful for the treatment of respiratory disorders such as asthma, chronic bronchitis and adult respiratory distress syndrome, as well as rheumatoid arthritis, ulcerative colitis, Crohn's disease, septic shock, nephritis, hepatitis, bacterial and viral infections, heart failure, atherosclerosis, myocardial infarction and stroke. Other exemplified compounds from this series of 2-oxo-1,2-dihydro-1,8-naphthyridine derivatives include the following:



Compound	R1	R2	R3	X	Formula
304503	3-Cl-Ph	3-CO2H-Ph	Me		C ₂₄ H ₁₉ ClN ₂ O ₃
304504	3-Cl-Ph	4-Pip	Me	fumarate	C ₂₂ H ₂₄ ClN ₃ O .C ₄ H ₄ O ₄
304505	3-Cl-Ph	CH2CH2CO2H	Cl		C ₁₉ H ₁₆ Cl ₂ N ₂ O ₃
304506	3-Cl-Ph	CH2CH2CO2H	CH=NOH		C ₂₀ H ₁₈ ClN ₃ O ₄
304507	cyclohexyl	CH2CH2CO2H	Me		C ₂₀ H ₂₆ N ₂ O ₃
304508	3-Me-Ph	CH2CH2CO2H	Me		C ₂₁ H ₂₂ N ₂ O ₃
304509	cyclohexyl	5-tetrazolyl- -CH2CH2	Me		C ₂₀ H ₂₆ N ₆ O

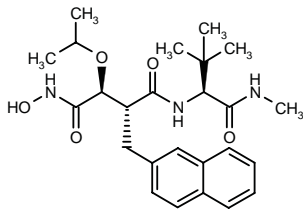
SOURCE – Yamanouchi.

REFERENCES

1. Iwata, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Naphthyridine derivs*. JP 2001192385, WO 0130779.

304512

*N*²-[4-(*N*-Hydroxyamino)-3(*S*)-isopropoxy-2(*R*)-(naphthalen-2-ylmethyl)succinyl]-*N*¹-methyl-*L*-*tert*-leucinamide



C25 H35 N3 O5; Mol wt: 457.5675

ACTION – Potent and selective inhibitor of the formation of soluble human CD23 (sCD23), with potential for the treatment or prophylaxis of conditions associated with excess production of sCD23 such as autoimmune diseases, inflammation and allergy. *In vitro*, compound was shown to potently inhibit sCD23 production in RPMI 8866 cell membranes (IC₅₀ = 60 nM), while it showed no effect on TNF-α release in lipopolysaccharide-stimulated human monocytes at 10 μM. In addition, it exhibited superior oral bioavailability compared to previously reported analogues in pharmacokinetic studies in monkeys.

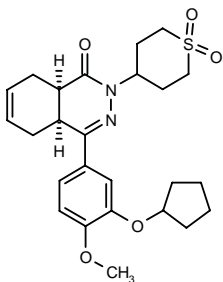
SOURCE – GlaxoSmithKline.

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1. Faller, A. and Ward, J.G. (SmithKline Beecham plc) *Hydroxamic acid deriv. as inhibitor of the formation of soluble human CD23*. WO 0130747.

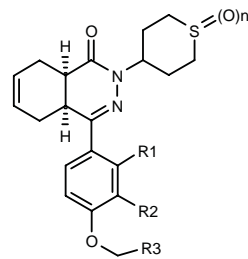
304517

cis-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-(1,1-dioxo-perhydrothiopyran-4-yl)-1,2,4a,5,8,8a-hexahydro-phthalazin-1-one



C25 H32 N2 O5 S; Mol wt: 472.6028

ACTION – Potent and selective inhibitor of phosphodiesterase type 4 (PDE4; -logIC₅₀ = 9.43), potentially useful for the treatment of inflammatory diseases of the airways (e.g., asthma), skin, CNS, intestine, eyes and joints, as well as for the treatment of erectile dysfunction. Other exemplified compounds from this series of phthalazinone derivatives include the following:



Compound	R1	R2	R3	n	Isomer	Formula
304518	-CH2C(Me)2O-		H	0	cis	C ₂₄ H ₃₀ N ₂ O ₃ S
304519	H	OMe	H	2	cis	C ₂₁ H ₂₆ N ₂ O ₅ S
304520	H	OMe	H	1	cis	C ₂₁ H ₂₆ N ₂ O ₄ S
304522	H	Cl	H	1	cis	C ₂₀ H ₂₃ ClN ₂ O ₃ S
304523	H	OEt	Me	2	cis	C ₂₃ H ₃₀ N ₂ O ₅ S
304524	-CH2C(Me)2O-		H	2	cis	C ₂₄ H ₃₀ N ₂ O ₅ S
304525	H	OMe	H	2	4aS,8aR	C ₂₁ H ₂₆ N ₂ O ₅ S

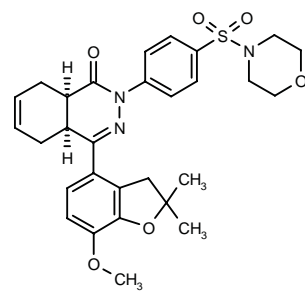
SOURCE – Byk Gulden.

REFERENCES

1. Hatzelmann, A. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Tetrahydrothiopyranphthalazinone derivs. as PDE4 inhibitors*. WO 0130777.

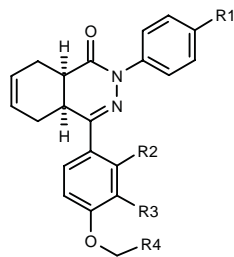
304527

cis-4-(7-Methoxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-4-yl)-2-[4-(morpholin-4-ylsulfonyl)phenyl]-1,2,4a,5,8,8a-hexahydrophthalazin-1-one



C29 H33 N3 O6 S; Mol wt: 551.6607

ACTION – Potent and selective inhibitor of phosphodiesterase type 4 (PDE4; -logIC₅₀ = 9.71), potentially useful for the treatment of inflammatory diseases of the airways (e.g., asthma), skin, CNS, intestine, eyes and joints, as well as for the treatment of erectile dysfunction. Other exemplified compounds from this series of phthalazinone derivatives are:



Compound	R1	R2	R3	R4	Formula
304528	4-morpholinyl-CO	H	OEt	Me	C ₂₉ H ₃₃ N ₃ O ₅
304529	4-morpholinyl-CO	-CH ₂ C(Me) ₂ O-	H	H	C ₃₀ H ₃₃ N ₃ O ₅
304530	4-thiomorpholinyl-CO	H	OMe	H	C ₂₇ H ₂₉ N ₃ O ₄ S
304531	4-morpholinyl-SO ₂	H	OEt	Me	C ₂₈ H ₃₃ N ₃ O ₆ S
304533	1,1-dioxo-4-thiomorpholinyl-CO	H	OEt	Me	C ₂₉ H ₃₃ N ₃ O ₆ S

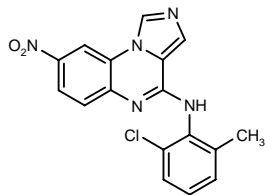
SOURCE – Byk Gulden.

REFERENCES

1. Hatzelmann, A. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Phthalazinone derivs. as PDE4 inhibitors*. WO 0130766.

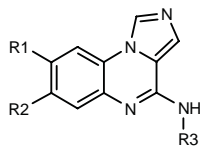
304688

N-(2-Chloro-6-methylphenyl)-8-nitroimidazo[1,5-a]quinoxalin-4-amine



C17 H12 Cl N5 O2; Mol wt: 353.7678

ACTION – Protein tyrosine kinase inhibitor particularly active against the Src family of kinases. Potentially useful for the treatment of transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, psoriasis and allergic diseases, among others, particularly asthma and allergic rhinitis. Other specifically claimed imidazoquinoxalines include the following:



Compound	R1	R2	R3	Formula
304690	H	Me	2-Br-Ph	C ₁₇ H ₁₃ BrN ₄
304691	H	H	2,6-(Br)2-4-Me-Ph	C ₁₇ H ₁₂ Br ₂ N ₄
304692	H	H	2-THF-CH ₂	C ₁₅ H ₁₆ N ₄ O
304693	OMe	OMe	2,4,6-(Me)3-3-Pyr	C ₂₀ H ₂₁ N ₅ O ₂
304695	cyclohexyl-CH ₂ NH	H	2-Cl-6-Me-Ph	C ₂₄ H ₂₆ ClN ₅
304696	H	NHAc	2-Cl-6-Me-Ph	C ₁₉ H ₁₆ ClN ₅ O
304697	OMe	OMe	2,6-(Br)2-4-F-Ph	C ₁₈ H ₁₃ Br ₂ FN ₄ O ₂
304698	OMe	4-morpholinyl-CH ₂ CH ₂ NH	2-Cl-6-F-Ph	C ₂₃ H ₂₄ ClFN ₆ O ₂

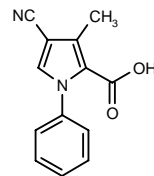
SOURCE – Bristol-Myers Squibb.

REFERENCES

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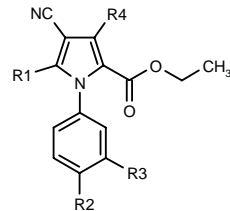
304780

4-Cyano-3-methyl-1-phenyl-1H-pyrrole-2-carboxylic acid



C13 H10 N2 O2; Mol wt: 226.2340

ACTION – An inhibitor of phosphodiesterase type 7 (PDE7) also reported to inhibit TNF-α production, potentially useful for the treatment of allergic disorders, asthma, chronic bronchitis, atopic dermatitis, psoriasis and other skin disorders, inflammatory and autoimmune disorders, Crohn’s disease, diabetes mellitus, osteoporosis, transplant rejection, cachexia, cancer, sepsis, memory impairment, atherosclerosis and AIDS. A representative compound from a series of substituted pyrrole derivatives, wherein the following compounds are also included:



Compound	R1	R2	R3	R4	Formula
304781	H	Cl	H	NH ₂	C ₁₄ H ₁₂ ClN ₃ O ₂
304782	NH ₂	H	H	Me	C ₁₅ H ₁₅ N ₃ O ₂
304783	H	H	H	NH ₂	C ₁₄ H ₁₃ N ₃ O ₂
304784	NH ₂	H	H	H	C ₁₄ H ₁₃ N ₃ O ₂
304785	H	OMe	Cl	NH ₂	C ₁₅ H ₁₄ ClN ₃ O ₃
304786	NH ₂	OMe	Cl	Me	C ₁₆ H ₁₆ ClN ₃ O ₃
304787	H	OCF ₃	H	NH ₂	C ₁₅ H ₁₂ F ₃ N ₃ O ₃

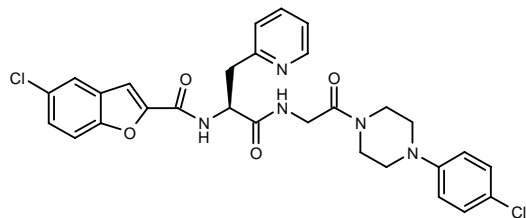
SOURCE – Merck KGaA.

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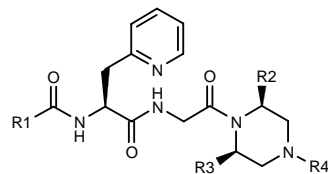
304822

5-Chloro-*N*-[1(*S*)-[*N*-[2-[4-(4-chlorophenyl)piperazin-1-yl]-2-oxoethyl]carbamoyl]-2-(2-pyridyl)ethyl]benzofuran-2-carboxamide



C29 H27 Cl2 N5 O4; Mol wt: 580.4693

ACTION – Agent for the treatment of adult respiratory distress syndrome, asthma, cardiovascular ischemia, myocarditis, heart failure, atherosclerosis, septic shock, diabetes, renal diseases, inflammatory bowel disease, pancreatitis, hepatitis, cerebral infarction, arthritis, osteoporosis, cancer, transplant rejection, sexual dysfunction and other nitric oxide (NO)-mediated diseases that acts by inhibiting the production of NO, as demonstrated in the murine macrophage cell line RAW 264.7 (100% inhibition at 1 μ M). Compounds of the invention are reported to markedly prolong rat cardiac allograft survival when given in combination with FK-506 (tacrolimus). A representative compound within a series of substituted dipeptides, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
304823	(E)-4-Cl-PhCH=CH	Me	H	Ph	C ₃₀ H ₃₂ ClN ₅ O ₃
304824	(E)-4-Cl-PhCH=CH	Me	Me	4-Me-Ph	C ₃₂ H ₃₆ ClN ₅ O ₃
304825	(E)-4-Cl-PhCH=CH	H	H	CH ₂ CH ₂ CF ₃	C ₂₆ H ₂₉ ClF ₃ N ₅ O ₃
304826	(E)-4-Cl-PhCH=CH	H	H	4-CF ₃ -Ph	C ₃₀ H ₂₉ ClF ₃ N ₅ O ₃
304827	5-Cl-2-benzofuryl	H	H	4-MeO-Ph	C ₃₀ H ₃₀ ClN ₅ O ₅

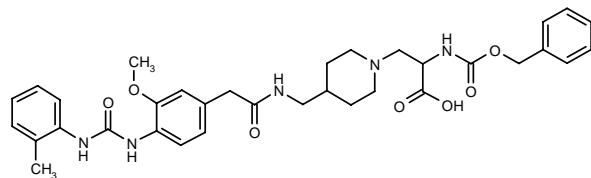
SOURCE – Fujisawa.

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1. Shima, I. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Substd. dipeptides having NOS inhibiting activity*. WO 0132690.

307213

2-(Benzyloxycarboxamido)-3-[4-[2-[3-methoxy-4-[3-(2-methylphenyl)ureido]phenyl]acetamidomethyl]piperidin-1-yl]propionic acid



C34 H41 N5 O7; Mol wt: 631.7259

ACTION – Nonpeptide VLA-4 ($\alpha_4\beta_1$) antagonist shown to potently inhibit VLA-4 binding to fibronectin (IC₅₀ = 7 nM), potentially useful for the treatment of bronchial asthma.

SOURCE – Aventis Pharma.

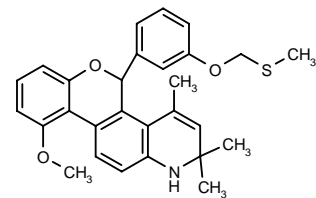
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2. Astles, P.C. et al. *Diamine containing VLA-4 antagonists*. Bioorg Med Chem 2001, 9(8): 2195.

307247

10-Methoxy-2,2,4-trimethyl-5-[3-(methylsulfanylmethoxy)-phenyl]-2,5-dihydro-1*H*-1-benzopyran[3,4-*f*]quinoline



C28 H29 N O3 S; Mol wt: 459.6071

ACTION – Selective nonsteroidal glucocorticoid receptor (GR) ligand with respective K_i values of 4.0, 3838 and 3115 nM for GR, mineralocorticoid and androgen receptors. The biological activity of the compound was similar to prednisolone in a reporter gene assay of glucocorticoid-mediated gene transcription (IC₅₀ = 9 and 8 nM, respectively), as well as *in vivo* in a rodent model of asthma, where it inhibited Sephadex-induced eosinophil influx with an ED₅₀ of 2.8 mg/kg p.o. versus ED₅₀ of 1.2 mg/kg p.o. for prednisolone. Potentially useful for the treatment of asthma.

SOURCES – Abbott; Ligand.

REFERENCES

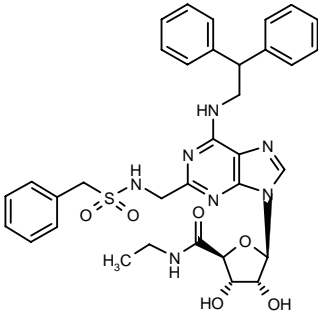
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TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY
DISEASES

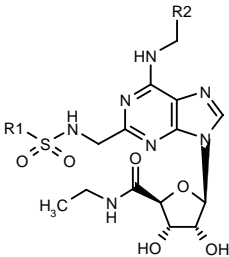
303857

2-(Benzylsulfonamidomethyl)-*N*-ethyl-*N*⁶-(2,2-diphenylethyl)adenosin-5'-uronamide



C34 H37 N7 O6 S; Mol wt: 671.7753

ACTION – Antiinflammatory agent, an adenosine A_{2A} receptor agonist particularly useful in the treatment of respiratory tract diseases such as adult respiratory distress syndrome (ARDS), bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. Also reported to be useful for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, inflammatory bowel disease and gastritis, among others. Other specifically claimed compounds from this series of purine derivatives are:



Compound	R1	R2	Formula
303858	Pr	CH(Ph)2	C ₃₀ H ₃₇ N ₇ O ₆ S
303859	i-Pr	CH(Ph)2	C ₃₀ H ₃₇ N ₇ O ₆ S
303860	Ph	CH(Ph)2	C ₃₃ H ₃₅ N ₇ O ₆ S
303861	4-Ph-Ph	CH(Ph)2	C ₃₉ H ₃₉ N ₇ O ₆ S
303862	1-Naph	CH(Ph)2	C ₃₇ H ₃₇ N ₇ O ₆ S
303863	2-Naph	CH(Ph)2	C ₃₇ H ₃₇ N ₇ O ₆ S
303864	Me	CH(Ph)2	C ₂₈ H ₃₃ N ₇ O ₆ S
303865	i-Bu	CH(Ph)2	C ₃₁ H ₃₉ N ₇ O ₆ S
303866	i-Bu	4-MeO-Ph	C ₂₅ H ₃₅ N ₇ O ₇ S
303867	1-Pip-CH2CH2	CH(Ph)2	C ₃₄ H ₄₄ N ₈ O ₆ S

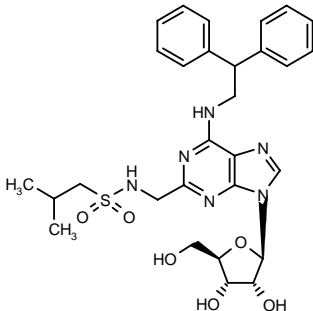
SOURCE – Pfizer.

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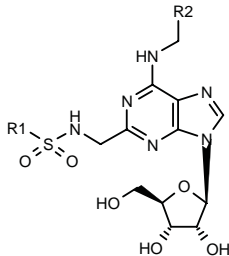
303868

2-(Isobutylsulfonamidomethyl)-*N*⁶-(2,2-diphenylethyl)-adenosine



C29 H36 N6 O6 S; Mol wt: 596.7054

ACTION – Antiinflammatory agent, an adenosine A_{2A} receptor agonist particularly useful in the treatment of respiratory tract diseases such as adult respiratory distress syndrome (ARDS), bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. Also reported to be useful for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, inflammatory bowel disease and gastritis, among others. Other specifically claimed compounds from this series of purine derivatives are:



Compound	R1	R2	Formula
303869	Ph	CH2Ph	C ₂₅ H ₂₈ N ₆ O ₆ S
303870	Ph	1-Naph	C ₂₈ H ₂₈ N ₆ O ₆ S
303871	cyclopentyl-N(i-Pr)CH2CH2	CH(Ph)2	C ₃₅ H ₄₇ N ₇ O ₆ S

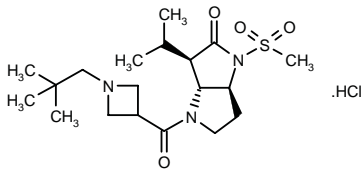
SOURCE – Pfizer.

REFERENCES

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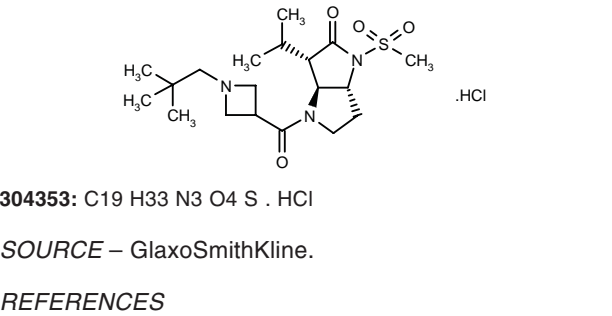
304352

(3*R*,3*aR*,6*aS*)-4-[1-(2,2-Dimethylpropyl)azetidin-3-yl-carbonyl]-3-isopropyl-1-(methylsulfonyl)perhydropyrrolo-[3,2-*b*]pyrrol-2-one hydrochloride



C19 H33 N3 O4 S . HCl; Mol wt: 436.0136

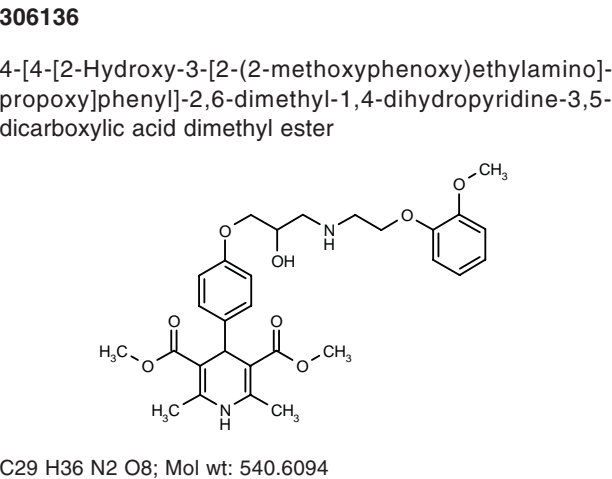
ACTION – An inhibitor of neutrophil elastase that is potentially useful for the treatment of inflammatory diseases, particularly chronic bronchitis and chronic obstructive pulmonary disease. This compound gave respective IC₅₀ values of 83 nM and 0.46 μM when tested for inhibition of human neutrophil elastase and human whole-blood elastase. Intracellular elastase inhibition was assessed *in vivo* in a hamster model of IL-8-induced lung infiltrates, showing a duration of action of at least 6 h at an oral dose of less than 10 mg/kg. Another specifically claimed compound is:



CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

LABEDIPINEDILOL B



ACTION – Third-generation dihydropyridine calcium channel blocker with additional α- and β-adrenoceptor-blocking activities, proven to produce long-lasting (> 1 h) and dose-dependent (0.5-3.0 mg/kg i.v.) hypotensive and bradycardic effects in anesthetized rats, and to inhibit (1.0 mg/kg i.v.) both the hypertensive effects of phenylephrine and the tachycardic effects of isoproterenol. *In vitro* in functional experiments, compound showed competitive antagonist activity at both β₁- and β₂-adrenoceptors (pA₂ = 6.61 and 6.48, respectively, for antagonizing the effect of isoproterenol in rat right atrium and guinea pig trachea) and at α₁-adrenoceptors (pA₂ = 7.55 in rat

thoracic aorta). It also demonstrated concentration-dependent calcium entry-blocking activity in rat preparations. Potentially useful as an antihypertensive and antianginal agent.

SOURCES – Development Center for Biotechnology, Taipei (TW); Kaohsiung Medical College, Kaohsiung (TW).

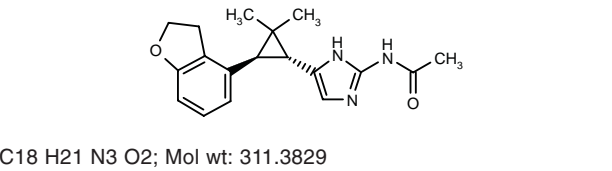
REFERENCES

1. Yeh, J.L. et al. *Third-generation dihydropyridine-type calcium channel blocker labedipinedilol-B displays α/β-adrenoceptor blocking activities*. Drug Dev Res 2001, 52(3): 462.

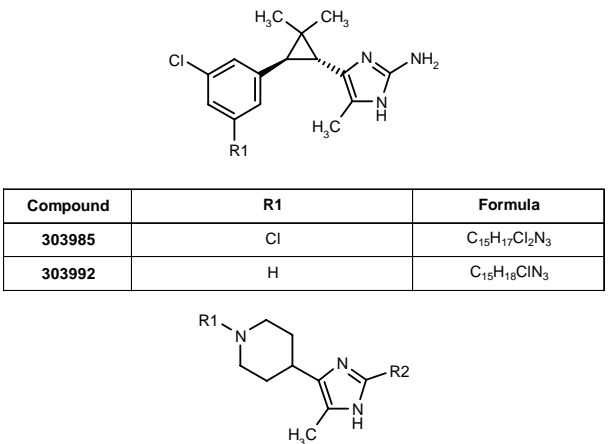
TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

303983

N-[5-[(1*R*,3*R*)-3-(2,3-Dihydrobenzofuran-4-yl)-2,2-dimethylcyclopropyl]-1*H*-imidazol-2-yl]acetamide

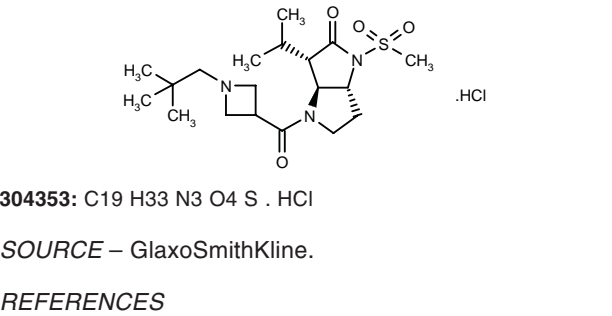


ACTION – Na⁺/H⁺ exchange (NHE) inhibitor, potentially useful as an antianginal, antiischemic and cardio-protective agent, as well as for the treatment of diseases associated with proliferation of smooth muscle cells, mesangial cells and fibroblasts, and renal diseases. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	Formula
303989	1-[2,3-(Cl)2-Ph]-3-Me-5-pyrazolyl	NH2	C ₁₉ H ₂₂ Cl ₂ N ₆
303990	3-(3-Me-Ph)-2-Pyr	H	C ₂₁ H ₂₄ N ₄
303995	5-[2,5-(Cl)2-Ph]-4-pyrimidinyl	H	C ₁₉ H ₁₉ Cl ₂ N ₅
303996	1-(4-Cl-3-Me-Ph)-5-tetrazolyl	H	C ₁₇ H ₂₀ ClN ₇
303997	1-(3-Cl-Ph)-3-CF3-5-pyrazolyl	H	C ₁₉ H ₁₉ ClF ₃ N ₅

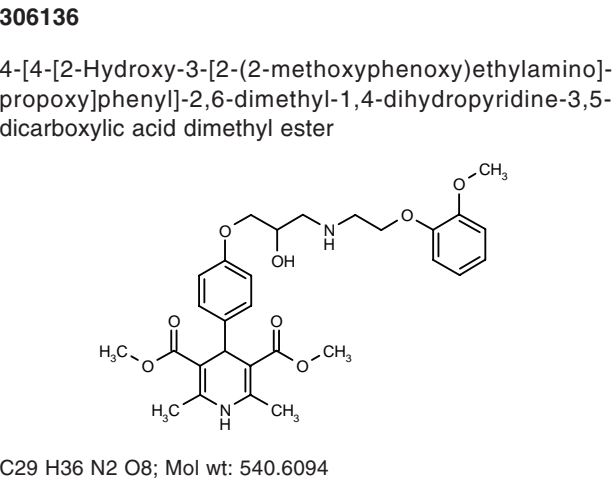
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

LABEDIPINEDILOL B



ACTION – Third-generation dihydropyridine calcium channel blocker with additional α- and β-adrenoceptor-blocking activities, proven to produce long-lasting (> 1 h) and dose-dependent (0.5-3.0 mg/kg i.v.) hypotensive and bradycardic effects in anesthetized rats, and to inhibit (1.0 mg/kg i.v.) both the hypertensive effects of phenylephrine and the tachycardic effects of isoproterenol. *In vitro* in functional experiments, compound showed competitive antagonist activity at both β₁- and β₂-adrenoceptors (pA₂ = 6.61 and 6.48, respectively, for antagonizing the effect of isoproterenol in rat right atrium and guinea pig trachea) and at α₁-adrenoceptors (pA₂ = 7.55 in rat

thoracic aorta). It also demonstrated concentration-dependent calcium entry-blocking activity in rat preparations. Potentially useful as an antihypertensive and antianginal agent.

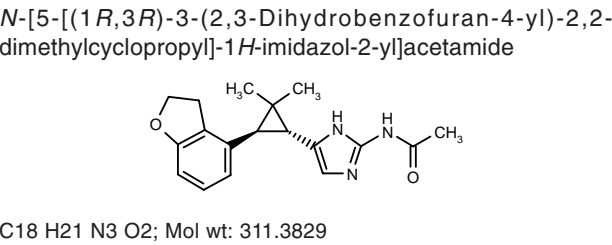
SOURCES – Development Center for Biotechnology, Taipei (TW); Kaohsiung Medical College, Kaohsiung (TW).

REFERENCES

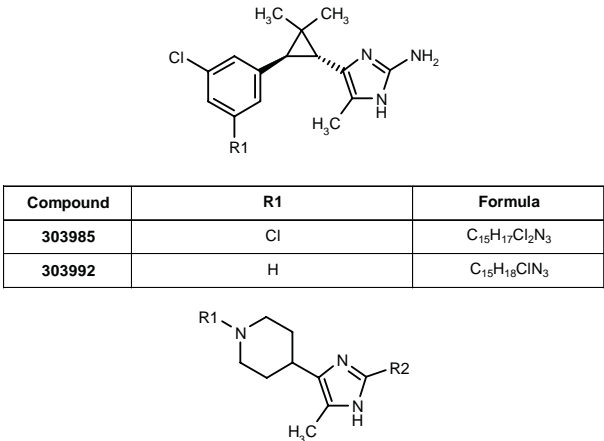
1. Yeh, J.L. et al. *Third-generation dihydropyridine-type calcium channel blocker labedipinedilol-B displays α/β-adrenoceptor blocking activities*. Drug Dev Res 2001, 52(3): 462.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

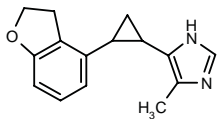
303983



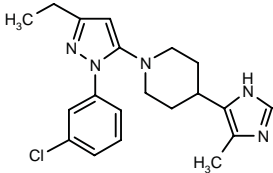
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Compound	R1	R2	Formula
303989	1-[2,3-(Cl)2-Ph]-3-Me-5-pyrazolyl	NH2	C ₁₉ H ₂₂ Cl ₂ N ₆
303990	3-(3-Me-Ph)-2-Pyr	H	C ₂₁ H ₂₄ N ₄
303995	5-[2,5-(Cl)2-Ph]-4-pyrimidinyl	H	C ₁₉ H ₁₉ Cl ₂ N ₅
303996	1-(4-Cl-3-Me-Ph)-5-tetrazolyl	H	C ₁₇ H ₂₀ ClN ₇
303997	1-(3-Cl-Ph)-3-CF3-5-pyrazolyl	H	C ₁₉ H ₁₉ ClF ₃ N ₅



303987: C15 H16 N2 O



303994: C20 H24 Cl N5

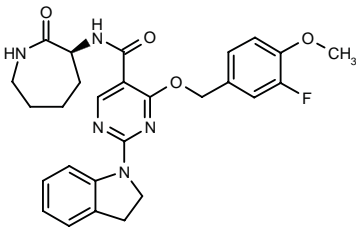
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Ahmad, S. et al. (Bristol-Myers Squibb Co.) *Heterocyclic sodium/proton exchange inhibitors and method.* WO 0127107.

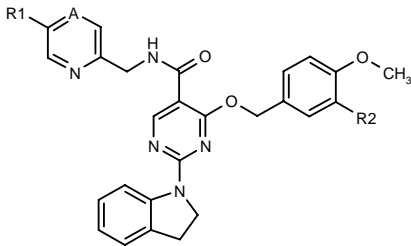
304291

2-(2,3-Dihydro-1*H*-indol-1-yl)-4-(3-fluoro-4-methoxybenzyloxy)-*N*-[2-oxoperhydroazepin-3(*S*)-yl]pyrimidine-5-carboxamide



C27 H28 F N5 O4; Mol wt: 505.5472

ACTION – Inhibitor of cGMP phosphodiesterase type 5 (PDE5), as demonstrated against recombinant human lung-derived PDE5 (IC₅₀ = 0.304 nM). This compound may be useful for the treatment of circulatory disorders such as angina pectoris and hypertension, allergic disorders and sexual dysfunction, among others. Other exemplified pyrimidine-5-carboxamide compounds include the following:



Compound	R1	R2	A	Formula
304292	Me	F	N	C ₂₇ H ₂₅ FN ₆ O ₃
304294	H	Cl	CH	C ₂₇ H ₂₄ ClN ₅ O ₃

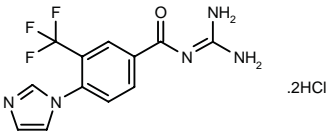
SOURCE – Takeda.

REFERENCES

1. Miwa, T. et al. (Takeda Chemical Industries, Ltd.) *Pyrimidine-5-carboxamide cpds., process for producing the same and use thereof.* JP 2001233875, WO 0127105.

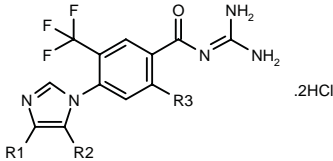
304542

*N*²-[4-(1*H*-Imidazol-1-yl)-3-(trifluoromethyl)benzoyl]guanidine dihydrochloride



C12 H10 F3 N5 O . 2HCl; Mol wt: 370.1608

ACTION – Antiarrhythmic agent with a cardioprotective component that inhibits the cellular Na⁺/H⁺-exchanger, potentially useful for the treatment and/or prophylaxis of myocardial infarction, angina pectoris, ischemia-induced arrhythmias, stroke, brain edema and shock states. It also inhibits the proliferation of cells such as fibroblasts and smooth muscle cells, and thus may have potential in the treatment of atherosclerosis, diabetic complications, cancer, fibrotic diseases and prostatic hyperplasia and hypertrophy. Other exemplified compounds from this series of heterocyclically substituted benzoylguanidines are:



Compound	R1	R2	R3	Formula
304543	Me	H	H	C ₁₃ H ₁₂ F ₃ N ₅ O.2HCl
304544	Me	Me	H	C ₁₄ H ₁₄ F ₃ N ₅ O.2HCl
304545	-CH=CHCH=CH-		H	C ₁₆ H ₁₂ F ₃ N ₅ O.2HCl
304546	-CH=C(Cl)C(Cl)=CH-		H	C ₁₆ H ₁₀ Cl ₂ F ₃ N ₅ O.2HCl
304547	-CH=C(Me)C(Me)=CH-		H	C ₁₈ H ₁₆ F ₃ N ₅ O.2HCl
304548	Me	Me	Me	C ₁₅ H ₁₆ F ₃ N ₅ O.2HCl
304549	-CH=CHCH=CH-		Me	C ₁₇ H ₁₄ F ₃ N ₅ O.2HCl
304550	-CH=CHCH=CH-		Cl	C ₁₆ H ₁₁ ClF ₃ N ₅ O.2HCl
304551	-CH=C(Cl)C(Cl)=CH-		Cl	C ₁₆ H ₉ Cl ₃ F ₃ N ₅ O.2HCl

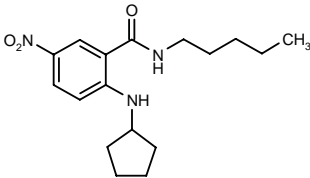
SOURCE – Aventis Pharma.

REFERENCES

1. Weichert, A. et al. (Aventis Pharma Deutschland GmbH) *Heterocyclically substd. benzoylguanidine, method for the production thereof, the use thereof as a medicament or means of diagnosis and a medicament containing the same.* DE 19950898, WO 0130761.

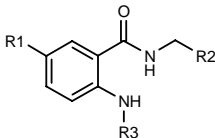
304624

2-(Cyclopentylamino)-5-nitro-*N*-pentylbenzamide



C17 H25 N3 O3; Mol wt: 319.4025

ACTION – Inhibitor of cGMP phosphodiesterase, particularly PDE5 (IC₅₀ < 10 nM for inhibition of human platelet cGMP PDE). Potentially useful for the treatment of angina, hypertension, congestive heart failure, renal failure, atherosclerosis, asthma, erectile dysfunction and diabetic complications, among others. Other exemplified anthranilic acid derivatives are:



Compound	R1	R2	R3	Formula
304625	NO2	cyclohexyl	cyclopentyl	C ₁₉ H ₂₇ N ₃ O ₃
304626	CF3	3-Cl-4-MeO-Ph	1-(HOCH2CH2)-3(S)-pyrrolidinyl	C ₂₂ H ₂₆ ClF ₃ N ₃ O ₃
304627	CN	3,4-(MeO)2-Ph	(1 <i>r</i> ,3 <i>t</i> ,5 <i>t</i>)-3,5-(MeO)2-cyclohexyl	C ₂₅ H ₃₁ N ₃ O ₅
304628	CN	3-Cl-4-MeO-Ph	(1 <i>R</i> ,4 <i>S</i>)-4-OH-2-cyclopentenyl	C ₂₁ H ₂₀ ClN ₃ O ₃
304629	CN	3-Cl-4-MeO-Ph	(1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)-3,4-(OH)2-cyclohexyl	C ₂₂ H ₂₄ ClN ₃ O ₄
304630	NO2	4-Me-3-Cl-Ph	cis-4-OH-cyclohexyl	C ₂₁ H ₂₄ ClN ₃ O ₄
304631	CN	3-Cl-4-MeO-Ph	C(Me)2CH2OH	C ₂₀ H ₂₂ ClN ₃ O ₃
304633	CN	3-CN-4-MeO-Ph	(<i>S</i>)-CH(Et)CH2OH	C ₂₁ H ₂₂ N ₄ O ₃
304634	CN	3-CN-4-MeO-Ph	trans-4-NH2-cyclohexyl	C ₂₃ H ₂₆ N ₅ O ₂
304635	CN	3-F-4-MeO-Ph	cis-4-OH-cyclohexyl	C ₂₂ H ₂₄ FN ₃ O ₃
304636	CN	3-CN-4-MeO-Ph	(1 <i>r</i> ,3 <i>c</i> ,4 <i>c</i>)-3,4-(OH)2-cyclohexyl	C ₂₃ H ₂₄ N ₄ O ₄
304637	CN	3-Cl-4-MeO-Ph	(1 <i>r</i> ,3 <i>t</i> ,5 <i>t</i>)-3-OH-5-MeO-cyclohexyl	C ₂₃ H ₂₆ ClN ₃ O ₄

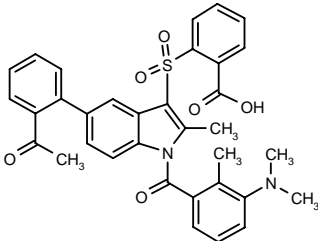
SOURCE – Fujisawa.

REFERENCES

1. Sawada, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Anthranilic acid derivs. as inhibitors of the cGMP-phosphodiesterase*. WO 0130745.

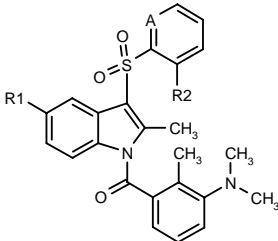
304893

2-[5-(2-Acetylphenyl)-1-[3-(dimethylamino)-2-methylbenzoyl]-2-methyl-1*H*-indol-3-ylsulfonyl]benzoic acid



C34 H30 N2 O6 S; Mol wt: 594.6850

ACTION – Agent for the treatment or prevention of circulatory diseases, inflammation, immunological diseases, allergic disorders, ocular diseases, diabetic complications, collagen diseases and obesity with potent and selective chymase-inhibitory activity, as demonstrated by IC₅₀ values of 11 nM and > 50 µM, respectively, against human recombinant chymase and bovine α-chymotrypsin. Other exemplified compounds from this series of indole derivatives include the following:



Compound	R1	R2	A	Formula
304894	CH2SO2Ph	H	CH	C ₃₂ H ₃₀ N ₂ O ₅ S ₂
304895	CH2SO2CH2Ph	H	CH	C ₃₃ H ₃₂ N ₂ O ₅ S ₂
304896	2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl	H	CH	C ₃₃ H ₂₈ N ₄ O ₅ S
304897	2-(NH2SO2)-Ph	CO2CH2Ph	N	C ₃₈ H ₃₄ N ₄ O ₇ S ₂
304898	2-Ac-Ph	CO2Me	CH	C ₃₆ H ₃₂ N ₂ O ₆ S
304899	3-Ac-Ph	CO2H	CH	C ₃₄ H ₃₀ N ₂ O ₆ S
304900	3-[MeCH(OH)]-Ph	CO2H	CH	C ₃₄ H ₃₂ N ₂ O ₆ S

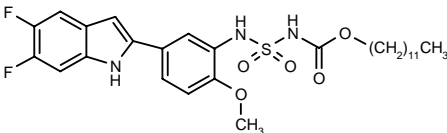
SOURCE – Wakunaga.

REFERENCES

1. Nishimura, K. et al. (Wakunaga Pharmaceutical Co., Ltd.) *Novel indole derivs. and drugs containing the same as the active ingredient*. WO 0132621.

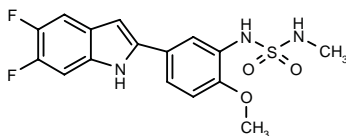
307748

N-[*N*-[5-(5,6-Difluoro-1*H*-indol-2-yl)-2-methoxyphenyl]-sulfamoyl]carbamic acid dodecyl ester



C28 H37 F2 N3 O5 S; Mol wt: 565.6783

ACTION – Potent sulfamyl inhibitor of 15-lipoxygenase (IC_{50} = 6 nM), potentially useful for the treatment of atherosclerosis. Another related compound is:



307749: C16 H15 F2 N3 O3 S

SOURCE – Pfizer.

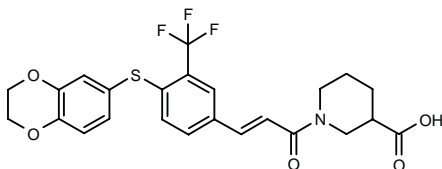
REFERENCES

1. Barvian, N.C. et al. *Sulfamyl inhibitors of 15-lipoxygenase*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 270.

A-304470

307241

1-[3-[4-(2,3-Dihydro-1,4-benzodioxin-6-ylsulfanyl)-3-(trifluoromethyl)phenyl]-2(*E*)-propenoyl]piperidine-3-carboxylic acid



C24 H22 F3 N O5 S; Mol wt: 493.4998

ACTION – Potent LFA-1 (leukocyte function-associated antigen-1)/ICAM-1 (intracellular adhesion molecule-1) antagonist with an IC_{50} of 0.025 μ M for inhibition of LFA-1/ICAM-1 binding and of 0.14 μ M for blockade of LFA-1-expressing JY-8 cell adherence to immobilized ICAM-1. Compound showed a favorable pharmacokinetic profile in rats and dogs, with respective oral bioavailabilities of 29 and 55%. *In vivo* in a rat model of myocardial ischemia and reperfusion, compound dose-dependently reduced myocardial infarct size from 68% in controls to 47% at 50 mg/kg i.v. Potentially useful for the treatment of myocardial infarction.

SOURCE – Abbott.

REFERENCES

1. Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds*. US 6110922, WO 0039081.

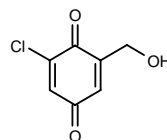
2. Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds*. WO 0059880.

3. Pei, Z. et al. *Discovery of potent antagonists of leukocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction. 3. Amide (C-ring) structure-activity relationship and improvement of overall properties of arylthio cinnamides*. J Med Chem 2001, 44(18): 2913.

FOM-8108

304933

2-Chloro-6-(hydroxymethyl)-1,4-benzoquinone



C7 H5 Cl O3; Mol wt: 172.5665

ACTION – A substance isolated from agonomycetes strain FOM-8108 (FERM P-17591) with sphingomyelinase-inhibitory activity, as demonstrated in *in vitro* studies. FOM-8108 was found to inhibit rat brain-derived neutral sphingomyelinase with an IC_{50} of 0.2 μ g/ml, but not human placenta-derived acid sphingomyelinase at 100 μ g/ml. This compound is expected to be useful for the treatment of arteriosclerosis, inflammation and diabetes.

SOURCE – Kitasato Institute, Tokyo (JP).

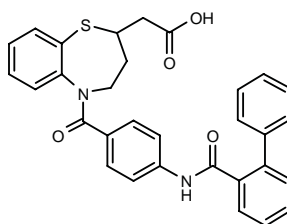
REFERENCES

1. Ohmura, S. et al. (Kitasato Institute) *Novel FOM-8108 substance and its preparation method*. JP 2001103990.

HEART FAILURE THERAPY

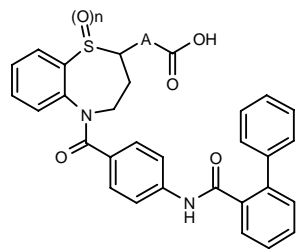
304806

2-[5-[4-(Biphenyl-2-ylcarboxamido)benzoyl]-2,3,4,5-tetrahydro-1,5-benzothiazepin-2-yl]acetic acid



C31 H26 N2 O4 S; Mol wt: 522.6224

ACTION – Vasopressin V_2 receptor antagonist, as demonstrated in binding assays by an IC_{50} value of 0.004 μ M for inhibition of [3 H]-arginine-8-vasopressin binding to cloned human V_2 receptors, compared to 16% inhibition of [3 H]-arginine-8-vasopressin binding to cloned human V_{1a} receptors at 0.1 μ M. Potentially useful for the treatment or prevention of conditions involving increased vascular resistance such as congestive heart failure, cardiac insufficiency, hypertension, coronary vasospasm, cardiac ischemia, liver cirrhosis, renal vasospasm, renal failure, cerebral edema and ischemia, stroke, thrombosis and water retention. Other specifically claimed compounds from this series of nonpeptide substituted benzothiazepines are:



Compound	A	n	Formula
304807	-CH2-	1	C ₃₁ H ₂₆ N ₂ O ₆ S
304808	-(CH2)2-	0	C ₃₂ H ₂₈ N ₂ O ₄ S

SOURCE – Ortho-McNeil.

REFERENCES

1. Urbanski, M.J. and Chen, R.H.K. (Ortho-McNeil Pharmaceutical, Inc.) *Nonpeptide substd. benzothiazepines as vasopressin antagonists*. WO 0132639.

NESIRITIDE

Prop INN, USAN

202811

1-32-Natriuretic factor (human brain, clone λhBNP57)

Seryl-prolyl-lysyl-methionyl-valyl-glutaminy-glycyl-seryl-glycyl-cysteiny-phenylalanyl-glycyl-arginyl-lysyl-methionyl-aspartyl-arginyl-isoleucyl-seryl-seryl-seryl-glycyl-leucyl-glycyl-cysteiny-lysyl-valyl-leucyl-arginyl-arginyl-histidine cyclic (S-3.10-S-3.26)-disulfide

Brain natriuretic peptide
BNP+
hBNP

C143 H244 N50 O42 S4; Mol wt: 3464.0730

ACTION – Human B-type natriuretic peptide.

INDICATION – Treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or upon minimal activity.

PRESENTATION – Single-use vials (1.5 ml) for i.v. injection containing 1.58 mg nesiritide as lyophilized powder.

PROPRIETARY NAME – Natrecor (US).

SOURCE – Scios.

RECENT REFERENCES

1. Abraham, W.T. et al. *Nesiritide (human B-type natriuretic peptide) improves symptoms and hemodynamics in NYHA class III and IV heart failure*. Cardiovasc Drugs Ther 1999, 13(1): Abst 135.

2. Abraham, W.T. et al. *Nesiritide (human B-type natriuretic peptide) improves symptoms and hemodynamics in NYHA class III and IV heart failure*. J Am Coll Cardiol 1999, 33(2, Suppl. A): 188A.

3. Bourge, R.C. et al. *Nesiritide improves hemodynamics in patients with acutely decompensated heart failure: Hemodynamic subgroup analysis*. Cardiovasc Drugs Ther 1999, 13(1): Abst 133.

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5. Brunner-La Rocca, H.P. et al. *Exogenous brain natriuretic peptide inhibits reflex systemic and regional sympathetic stimulation in healthy humans*. J Hypertens 2000, 18(Suppl. 2): Abst P2.177.

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33. *Scios and Bayer end commercial alliance for Natrecor.* DailyDrugNews.com (Daily Essentials) 1999, June 11.

34. *Scios begins patient enrollment in phase III Natrecor trial.* DailyDrugNews.com (Daily Essentials) 1999, Oct 28.

35. *Scios licenses BNP technology to Abbott.* DailyDrugNews.com (Daily Essentials) 1997, June 4.

36. *Scios updates status, reviews progress of lead products.* DailyDrugNews.com (Daily Essentials) 2001, April 30.

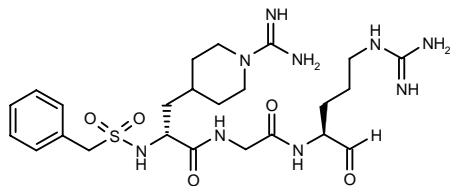
*Drug Data Rep 1994, 016(04): 0337.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

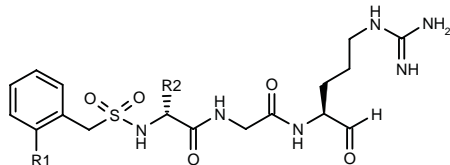
303899

N-(Benzylsulfonyl)-3-(1-amidinopiperidin-4-yl)-D-alanyl-glycyl-L-argininal



C24 H39 N9 O5 S; Mol wt: 565.6961

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of factor Xa (IC₅₀ = 0.825 nM) with high selectivity relative to other serine proteases such as thrombin (IC₅₀ > 2500 nM; selectivity index > 3,030) and trypsin (IC₅₀ = 169 nM; selectivity index = 204.8). Other compounds from this series of peptidyl aldehydes include the following:



Compound	R1	R2	Formula
303901	H	1-[NH2C(=NH)]-3-Pip-CH2	C ₂₄ H ₃₉ N ₉ O ₅ S
303904	CO2Me	1-[NH2C(=NH)]-3-Pip-CH2	C ₂₆ H ₄₁ N ₉ O ₇ S
303906	CO2Me	1-[NH2C(=NH)]-4-Pip-CH2	C ₂₆ H ₄₁ N ₉ O ₇ S
303907	1-t-Bu-5-tetrazolyl	1-[NH2C(=NH)]-4-Pip-CH2	C ₂₉ H ₄₇ N ₁₃ O ₅ S
303909	5-tetrazolyl	1-[NH2C(=NH)]-4-Pip-CH2	C ₂₈ H ₃₉ N ₁₃ O ₅ S
303910	H	1-[C(=NH)NH2]-4-Pip	C ₂₃ H ₃₇ N ₉ O ₅ S

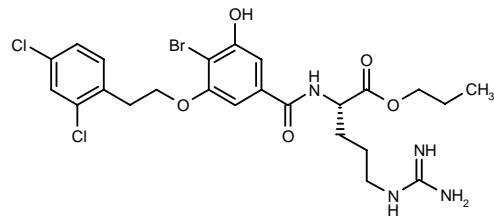
SOURCE – Corvas.

REFERENCES

1. Semple, J.E. et al. (Corvas International, Inc.) *Inhibitors of factor Xa having an arginine or arginine aldehyde mimic.* WO 0127141.

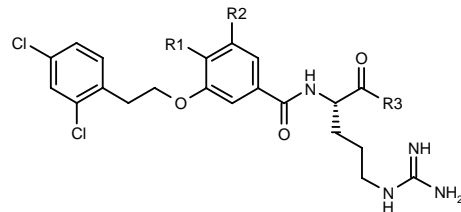
304287

N-[4-Bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxy-benzoyl]-L-arginine propyl ester



C24 H29 Br Cl2 N4 O5; Mol wt: 604.3261

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of factor Xa (K_i = 0.021 and > 200 μM, respectively, for inhibition of human factor Xa and factor VIIa). Other exemplified compounds from this series of N-guanidinoalkylamides include the following:



Compound	R1	R2	R3	Formula
304293	Br	OH	3-Pyr-CH2NH	C ₂₇ H ₂₉ BrCl ₂ N ₆ O ₄
304295	Br	OH	N(Me)2	C ₂₃ H ₂₈ BrCl ₂ N ₅ O ₄
304296	Br	OH	OH	C ₂₁ H ₂₃ BrCl ₂ N ₄ O ₅
304297	OMe	H	N(Me)2	C ₂₄ H ₃₁ Cl ₂ N ₅ O ₄
304298	OMe	H	OPr	C ₂₈ H ₃₂ Cl ₂ N ₄ O ₅

Certain compounds of the invention exhibit dual factor Xa- and factor VIIa-inhibitory activity.

SOURCE – Aventis Pharma.

REFERENCES

1. Klinger, O. et al. (Aventis Pharma Deutschland GmbH) *Novel N-guanidino-alkylamides, their preparation, their use, and pharmaceutical preparations comprising them.* EP 1095933, WO 0132611.

31. *Pharmacoeconomic evaluation of Natrecor for treatment of acute heart failure.* DailyDrugNews.com (Daily Essentials) 2001, March 22.

32. *Phase III results reported for Natrecor in CHF.* DailyDrugNews.com (Daily Essentials) 2000, Nov 22.

33. *Scios and Bayer end commercial alliance for Natrecor.* DailyDrugNews.com (Daily Essentials) 1999, June 11.

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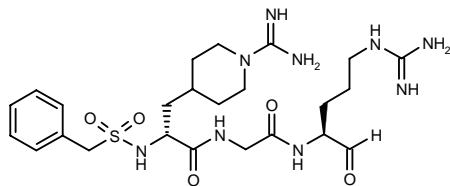
*Drug Data Rep 1994, 016(04): 0337.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

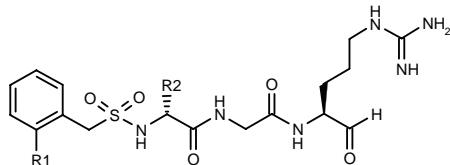
303899

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C24 H39 N9 O5 S; Mol wt: 565.6961

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of factor Xa (IC₅₀ = 0.825 nM) with high selectivity relative to other serine proteases such as thrombin (IC₅₀ > 2500 nM; selectivity index > 3,030) and trypsin (IC₅₀ = 169 nM; selectivity index = 204.8). Other compounds from this series of peptidyl aldehydes include the following:



Compound	R1	R2	Formula
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303907	1-t-Bu-5-tetrazolyl	1-[NH2C(=NH)]-4-Pip-CH2	C ₂₉ H ₄₇ N ₁₃ O ₅ S
303909	5-tetrazolyl	1-[NH2C(=NH)]-4-Pip-CH2	C ₂₈ H ₃₉ N ₁₃ O ₅ S
303910	H	1-[C(=NH)NH2]-4-Pip	C ₂₃ H ₃₇ N ₉ O ₅ S

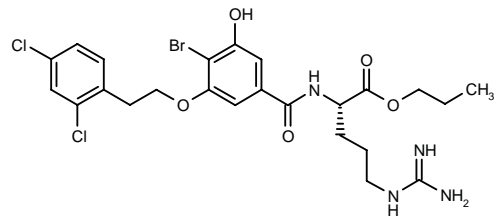
SOURCE – Corvas.

REFERENCES

1. Semple, J.E. et al. (Corvas International, Inc.) *Inhibitors of factor Xa having an arginine or arginine aldehyde mimic.* WO 0127141.

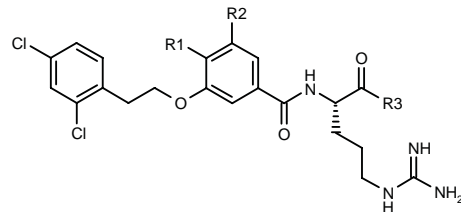
304287

N-[4-Bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxy-benzoyl]-L-arginine propyl ester



C24 H29 Br Cl2 N4 O5; Mol wt: 604.3261

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of factor Xa (K_i = 0.021 and > 200 μM, respectively, for inhibition of human factor Xa and factor VIIa). Other exemplified compounds from this series of N-guanidinoalkylamides include the following:



Compound	R1	R2	R3	Formula
304293	Br	OH	3-Pyr-CH2NH	C ₂₇ H ₂₉ BrCl ₂ N ₆ O ₄
304295	Br	OH	N(Me)2	C ₂₃ H ₂₈ BrCl ₂ N ₅ O ₄
304296	Br	OH	OH	C ₂₁ H ₂₃ BrCl ₂ N ₄ O ₅
304297	OMe	H	N(Me)2	C ₂₄ H ₃₁ Cl ₂ N ₅ O ₄
304298	OMe	H	OPr	C ₂₈ H ₃₂ Cl ₂ N ₄ O ₅

Certain compounds of the invention exhibit dual factor Xa- and factor VIIa-inhibitory activity.

SOURCE – Aventis Pharma.

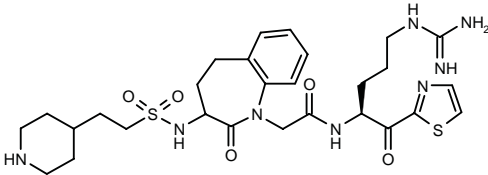
REFERENCES

1. Klinger, O. et al. (Aventis Pharma Deutschland GmbH) *Novel N-guanidino-alkylamides, their preparation, their use, and pharmaceutical preparations comprising them.* EP 1095933, WO 0132611.

304377

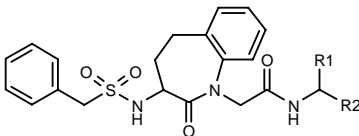
N-[4-Guanidino-1 (*S*)-(thiazol-2-ylcarbonyl)butyl]-2-[2-oxo-3-[2-(4-piperidiny)ethylsulfonamido]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetamide

2-[*N*^α]-[2-[2-Oxo-3-[2-(4-piperidiny)ethylsulfonamido]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetyl]-L-arginyl]thiazole



C28 H40 N8 O5 S2; Mol wt: 632.8070

ACTION – Anticoagulant, a potent factor Xa inhibitor with selectivity versus other coagulation- and fibrinolysis-related proteases. Potentially useful for the treatment of thrombosis, stroke and myocardial infarction. Other exemplified fused bicyclic lactam compounds include the following:



Compound	R1	R2	Formula
304378	2-thiazolyl-CO	(CH2)3NHC(=NH)NH2	C ₂₈ H ₃₃ N ₇ O ₅ S ₂
304379	COCNHCH2CH2Ph	(S)-(CH2)3NHC(=NH)NH2	C ₃₄ H ₄₁ N ₇ O ₆ S
304381	4-[NH2C(=NH)]-Ph	H	C ₂₇ H ₂₉ N ₅ O ₄ S

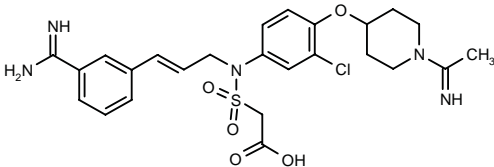
SOURCE – COR Therapeutics.

REFERENCES

1. Scarborough, R. and Zhu, B.-Y. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors*. US 6228854.

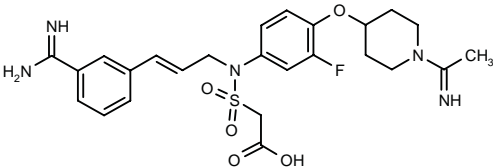
304955

2-[*N*-[3-(3-Amidinophenyl)-2(*E*)-propenyl]-*N*-[3-chloro-4-[1-(1-iminoethyl)piperidin-4-yloxy]phenyl]sulfamoyl]acetic acid



C25 H30 Cl N5 O5 S; Mol wt: 548.0610

ACTION – Anticoagulant that selectively inhibits factor Xa (IC₅₀ = 7.4 nM) versus trypsin (IC₅₀ = 520 nM). Potentially useful for the treatment of blood coagulation-related disorders such as cerebral or myocardial infarction and peripheral circulatory disorders. Another exemplified benzamidine derivative is:



304956: C25 H30 F N5 O5 S

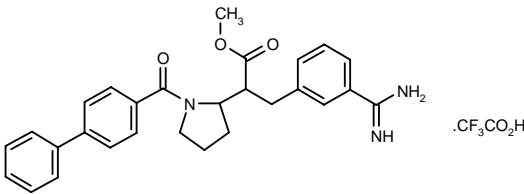
SOURCE – Sankyo.

REFERENCES

1. Fujimoto, K. et al. (Sankyo Co., Ltd.) *Benzamidine derivs*. WO 0130756.

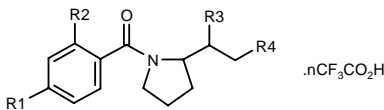
305038

3-(3-Amidinophenyl)-2-[1-(biphenyl-4-ylcarbonyl)pyrrolidin-2-yl]propionic acid methyl ester trifluoroacetate

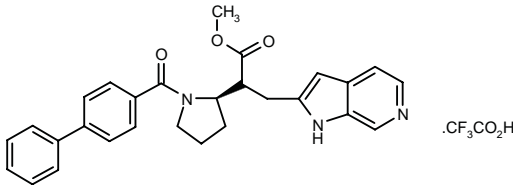


C28 H29 N3 O3 . C2 H F3 O2; Mol wt: 569.5770

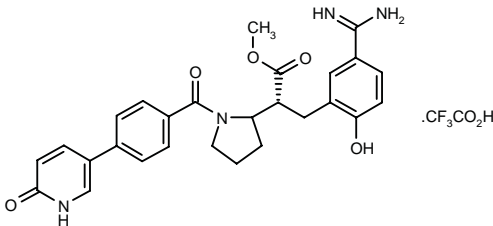
ACTION – Anticoagulant, a factor Xa inhibitor that has been reported to exhibit marked pharmacological activity in experimental venous and arterial thrombosis models in rabbits. Other specifically claimed *N*-acyl-pyrrolidin-2-ylalkylbenzamide derivatives include the following:



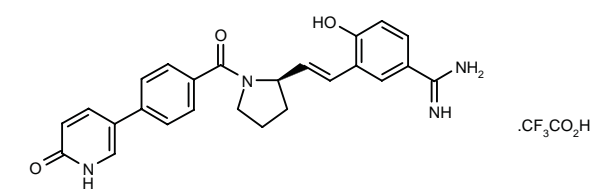
Compound	R1	R2	R3	R4	n	Formula
305040	Ph	CH2NH2	CO2Me	3-[NH2C(=NH)]-PhCH2	2	C ₂₉ H ₃₂ N ₄ O ₃ .2C ₂ HF ₃ O ₂
305042	2-oxo-1,2-dihydro-5-Pyr	H	CO2Me	3-[NH2C(=NH)]-PhCH2	1	C ₂₇ H ₂₈ N ₄ O ₄ .C ₂ HF ₃ O ₂
305044	Ph	H	CO2Me	4-[C(=NH)NH2]-PhCH2	1	C ₂₈ H ₂₉ N ₃ O ₃ .C ₂ HF ₃ O ₂
305048	2-oxo-1,2-dihydro-5-Pyr	H	H	3-[NH2C(=NH)]-Ph	1	C ₂₆ H ₂₆ N ₄ O ₂ .C ₂ HF ₃ O ₂



305045: C28 H27 N3 O3 . C2 H F3 O2



305046: C27 H28 N4 O5 . C2 H F3 O2



305049: C₂₅ H₂₄ N₄ O₃ . C₂ H F₃ O₂

SOURCE – Aventis Pharma.

REFERENCES

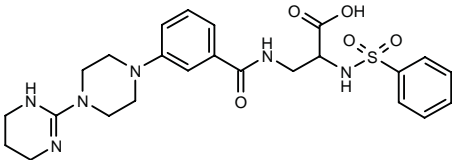
1. Czekaj, M. et al. (Aventis Pharma Deutschland GmbH) *N-Acylpyrrolidin-2-ylalkylbenzamide derivs. as inhibitors of factor Xa*. WO 0134567.

ANTIPLATELET THERAPY

304281

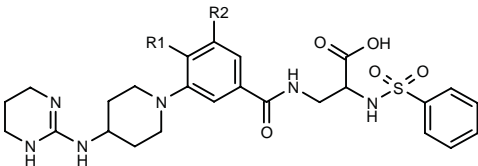
N-Phenylsulfonyl-3-[3-[4-(1,4,5,6-tetrahydropyrimidin-2-yl)piperazin-1-yl]benzamido]-DL-alanine

2-(Phenylsulfonamido)-3-[3-[4-(1,4,5,6-tetrahydro-pyrimidin-2-yl)piperazin-1-yl]benzamido]propionic acid



C₂₄ H₃₀ N₆ O₅ S; Mol wt: 514.6040

ACTION – Dual integrin $\alpha_v\beta_3$ and fibrinogen gpIIb/IIIa receptor antagonist (IC₅₀ = 1.3 and 2.0 nM, respectively). This compound was also reported to inhibit human platelet aggregation and is potentially useful for the treatment of cardiovascular and cerebrovascular disorders, thromboembolic disorders, neovascularization-related disorders, cancer, immune diseases and bone disorders. Other exemplified benzoic acid derivatives include the following:



Compound	R1	R2	Formula
304282	F	H	C ₂₅ H ₃₁ FN ₆ O ₅ S
304283	H	CF ₃	C ₂₆ H ₃₁ F ₃ N ₆ O ₅ S

SOURCE – Meiji Seika.

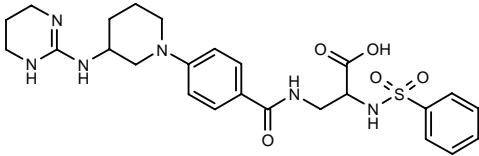
REFERENCES

1. Ajito, K. et al. (Meiji Seika Kaisha, Ltd.) *m-Substd. benzoic acid derivs. exhibiting integrin $\alpha_v\beta_3$ antagonism*. WO 0127090.

304286

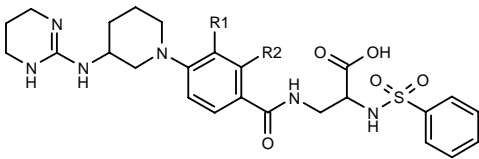
N-Phenylsulfonyl-3-[4-[3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)piperidin-1-yl]benzamido]-DL-alanine

2-(Phenylsulfonamido)-3-[4-[3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)piperidin-1-yl]benzamido]propionic acid



C₂₅ H₃₂ N₆ O₅ S; Mol wt: 528.6308

ACTION – Dual integrin $\alpha_v\beta_3$ and fibrinogen gpIIb/IIIa receptor antagonist (IC₅₀ = 1.0 and 1.1 nM or less, respectively). This compound was also reported to inhibit human platelet aggregation (IC₅₀ = 56 nM) and is potentially useful for the treatment of cardiovascular and cerebrovascular disorders, thromboembolic disorders, neovascularization-related disorders, cancer, immune diseases and bone disorders. Other exemplified 3-aminopiperidine derivatives include the following:



Compound	R1	R2	Formula
304288	F	H	C ₂₅ H ₃₁ FN ₆ O ₅ S
304290	H	F	C ₂₆ H ₃₁ FN ₆ O ₅ S

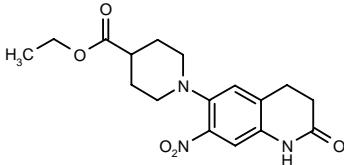
SOURCE – Meiji Seika.

REFERENCES

1. Ishikawa, M. et al. (Meiji Seika Kaisha, Ltd.) *3-Aminopiperidine derivs. as integrin $\alpha_v\beta_3$ antagonists*. WO 0127082.

306303

1-(7-Nitro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)piperidine-4-carboxylic acid ethyl ester



C₁₇ H₂₁ N₃ O₅; Mol wt: 347.3689

ACTION – Selective antiplatelet agent (IC₅₀ = 3.4 μ M against ADP-induced aggregation of rabbit platelet-rich plasma) with weak cardiotonic and chronotropic effects.

SOURCE – Kissei.

REFERENCES

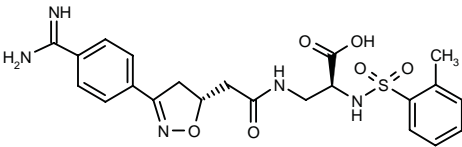
1. Ujile, S. et al. (Kissei Pharmaceutical Co., Ltd.) *Piperidino-3,4-dihydrocarbostyryl derivs.* JP 1994298756.

2. Iyobe, A. et al. *Studies on new platelet aggregation inhibitors 1. Synthesis of 7-nitro-3,4-dihydroquinoline-2(1H)-one derivatives.* Chem Pharm Bull 2001, 49(7): 822.

SD-270^{2,3}

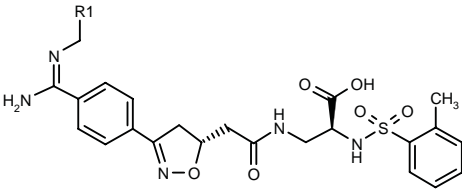
306969

3-[2-[3-(4-Amidinophenyl)-4,5-dihydroisoxazol-5(R)-yl]acetamido]-N-(2-methylphenylsulfonyl)-L-alanine



C22 H25 N5 O6 S; Mol wt: 487.5345

ACTION – Antiplatelet agent, a platelet gpIIb/IIIa receptor antagonist shown to inhibit platelet aggregation in human platelet-rich plasma (IC₅₀ = 54 nM) and to exhibit high *ex vivo* potency in a canine model, where the dose of 0.025 mg/kg i.v. induced strong (100%) and long-lasting (up to 24 h) inhibition of platelet aggregation. Other selected compounds from this series of amidine isoxazolines are:



Compound	R1	Formula
306970 ^{1,3}	Me	C ₂₄ H ₂₉ N ₅ O ₆ S
306971 ^{1,3}	Pr	C ₂₆ H ₃₃ N ₅ O ₆ S
307328 ^{1,3}	2-MeO-Ph	C ₃₀ H ₃₃ N ₅ O ₇ S

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Wityak, J. et al. (DuPont Pharmaceuticals Co.) *Novel isoxazoline and isoxazole fibrinogen receptor antagonists.* EP 0730590, EP 0832076, JP 1997505590, JP 1999504651, US 5849736, WO 9514683, WO 9638426.

2. Olson, R.E. et al. *Orally active isoxazoline glycoprotein IIb/IIIa antagonists with extended duration of action.* J Med Chem 1999, 42(7): 1178.

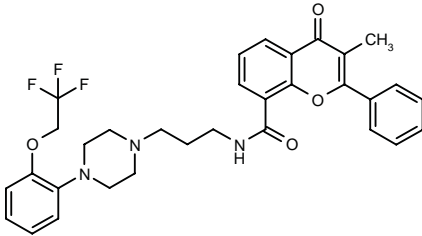
3. Sielecki, T.M. et al. *Synthesis and pharmacology of modified amidine isoxazoline glycoprotein IIb/IIIa receptor antagonists.* Bioorg Med Chem Lett 2001, 11(16): 2201.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

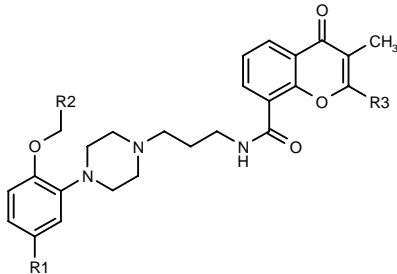
304221

3-Methyl-4-oxo-2-phenyl-N-[3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-4H-1-benzopyran-8-carboxamide



C32 H32 F3 N3 O4; Mol wt: 579.6158

ACTION – Selective α_{1A} -adrenoceptor antagonist (K_i = 0.07 nM vs. 6.00 and 3.38 nM, respectively, against α_{1B} - and α_{1D} -adrenoceptors) with additional selectivity relative to the 5-HT_{1A} receptor (K_i = 0.71 nM). α_1 -Adrenoceptor-antagonist activity was demonstrated in functional assays by its ability to block noradrenaline-induced contractions of rabbit aorta pretreated with chloroethylclonidine (α_{1L} -adrenoceptor; pK_b = 8.19). *In vivo*, compound exhibited greater relative potency in inhibiting noradrenaline-induced contractions of the urethra (ID₅₀ = 4.9 μ g/kg i.v.) than in lowering diastolic blood pressure (DBP) in dogs (ED₂₅ = 3001 μ g/kg i.v.; DBP/urethra ratio = 612). Potentially useful for the treatment of obstructive syndromes of the lower urinary tract including benign prostatic hyperplasia (BPH), while being devoid of hypotensive activity. Other exemplified compounds from this series of benzopyran derivatives include the following:



Compound	R1	R2	R3	Formula
304222	Cl	H	CONH2	C ₂₆ H ₂₉ ClN ₄ O ₅
304223	Cl	H	CO2Et	C ₂₈ H ₃₂ ClN ₃ O ₆
304224	CN	H	Ph	C ₃₂ H ₃₂ N ₄ O ₄
304225	Cl	CF3	Ph	C ₃₂ H ₃₁ ClF ₃ N ₃ O ₄

SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Benzopyran derivs.* WO 0129022.

SOURCE – Kissei.

REFERENCES

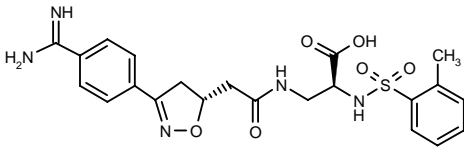
1. Ujile, S. et al. (Kissei Pharmaceutical Co., Ltd.) *Piperidino-3,4-dihydrocarbostyryl derivs.* JP 1994298756.

2. Iyobe, A. et al. *Studies on new platelet aggregation inhibitors 1. Synthesis of 7-nitro-3,4-dihydroquinoline-2(1H)-one derivatives.* Chem Pharm Bull 2001, 49(7): 822.

SD-270^{2,3}

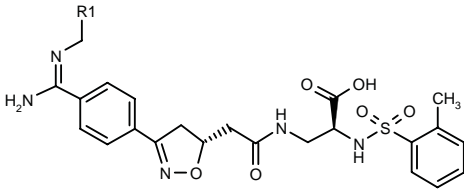
306969

3-[2-[3-(4-Amidinophenyl)-4,5-dihydroisoxazol-5(R)-yl]acetamido]-N-(2-methylphenylsulfonyl)-L-alanine



C22 H25 N5 O6 S; Mol wt: 487.5345

ACTION – Antiplatelet agent, a platelet gpIIb/IIIa receptor antagonist shown to inhibit platelet aggregation in human platelet-rich plasma (IC₅₀ = 54 nM) and to exhibit high *ex vivo* potency in a canine model, where the dose of 0.025 mg/kg i.v. induced strong (100%) and long-lasting (up to 24 h) inhibition of platelet aggregation. Other selected compounds from this series of amidine isoxazolines are:



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306971 ^{1,3}	Pr	C ₂₆ H ₃₃ N ₅ O ₆ S
307328 ^{1,3}	2-MeO-Ph	C ₃₀ H ₃₃ N ₅ O ₇ S

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Wityak, J. et al. (DuPont Pharmaceuticals Co.) *Novel isoxazoline and isoxazole fibrinogen receptor antagonists.* EP 0730590, EP 0832076, JP 1997505590, JP 1999504651, US 5849736, WO 9514683, WO 9638426.

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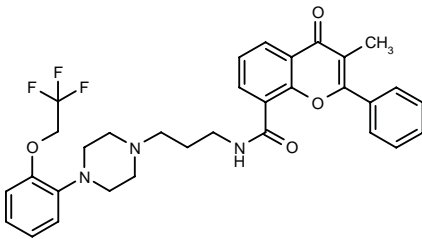
3. Sielecki, T.M. et al. *Synthesis and pharmacology of modified amidine isoxazoline glycoprotein IIb/IIIa receptor antagonists.* Bioorg Med Chem Lett 2001, 11(16): 2201.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

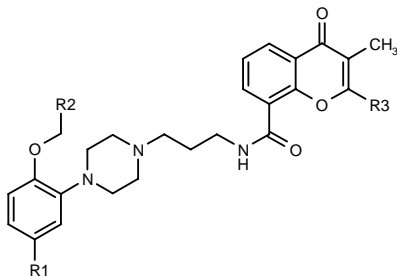
304221

3-Methyl-4-oxo-2-phenyl-N-[3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-4H-1-benzopyran-8-carboxamide



C32 H32 F3 N3 O4; Mol wt: 579.6158

ACTION – Selective α_{1A} -adrenoceptor antagonist (K_i = 0.07 nM vs. 6.00 and 3.38 nM, respectively, against α_{1B} - and α_{1D} -adrenoceptors) with additional selectivity relative to the 5-HT_{1A} receptor (K_i = 0.71 nM). α_1 -Adrenoceptor-antagonist activity was demonstrated in functional assays by its ability to block noradrenaline-induced contractions of rabbit aorta pretreated with chloroethylclonidine (α_{1L} -adrenoceptor; pK_b = 8.19). *In vivo*, compound exhibited greater relative potency in inhibiting noradrenaline-induced contractions of the urethra (ID₅₀ = 4.9 μ g/kg i.v.) than in lowering diastolic blood pressure (DBP) in dogs (ED₂₅ = 3001 μ g/kg i.v.; DBP/urethra ratio = 612). Potentially useful for the treatment of obstructive syndromes of the lower urinary tract including benign prostatic hyperplasia (BPH), while being devoid of hypotensive activity. Other exemplified compounds from this series of benzopyran derivatives include the following:



Compound	R1	R2	R3	Formula
304222	Cl	H	CONH2	C ₂₆ H ₂₉ ClN ₄ O ₅
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304224	CN	H	Ph	C ₃₂ H ₃₂ N ₄ O ₄
304225	Cl	CF3	Ph	C ₃₂ H ₃₁ ClF ₃ N ₃ O ₄

SOURCE – Recordati.

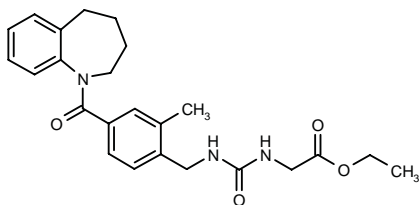
REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Benzopyran derivs.* WO 0129022.

TREATMENT OF URINARY INCONTINENCE

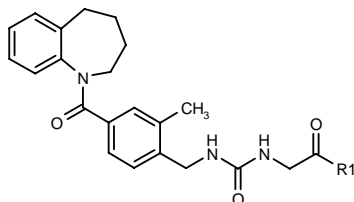
304132

2-[3-[2-Methyl-4-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-ylcarbonyl)benzyl]ureido]acetic acid ethyl ester



C₂₄ H₂₉ N₃ O₄; Mol wt: 423.5101

ACTION – Selective vasopressin V₂ receptor agonist proven to decrease urine output by 74% at 1 h post-administration when given to Brattleboro rats at 1 mg/kg p.o. Potentially useful for the treatment of nocturnal enuresis, nocturia, diabetes insipidus, urinary incontinence and bleeding disorders. Other exemplified bicyclic compounds include the following:



Compound	R1	Formula
304133	OH	C ₂₂ H ₂₅ N ₃ O ₄
304134	N(Me) ₂	C ₂₄ H ₃₀ N ₄ O ₃
304135	1-Pip	C ₂₇ H ₃₄ N ₄ O ₃

SOURCE – Ferring.

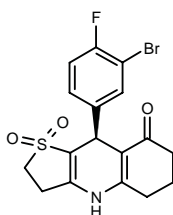
REFERENCES

1. Ashworth, D.M. et al. (Ferring BV Group Holding) *Bicyclic vasopressin agonists*. WO 0129005.

A-278637¹⁻⁴

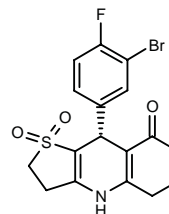
304414

(-)-9(*S*)-(3-Bromo-4-fluorophenyl)-2,3,4,5,6,7,8,9-octahydrothieno[3,2-*b*]quinoline-8-one 1,1-dioxide



C₁₇ H₁₅ Br F N O₃ S; Mol wt: 412.2775

ACTION – Bladder-selective potassium K_{ATP} channel opener proven to strongly reduce membrane potential responses in bladder smooth muscle cells (EC₅₀ = 96 nM) and to inhibit spontaneous contractions in pig bladder strips (IC₅₀ = 27 nM). In a pig model of bladder outlet obstruction, compound dose-dependently suppressed unstable myogenic contractions (AUC ED_{30%} = 3 nmol/kg i.v.) being more potent than ZD-6169 and WAY-133537; it also showed higher bladder selectivity versus blood pressure lowering compared with the reference compounds. Potentially useful for the treatment of overactive bladder. Another related compound is:



A-278636 [278034]:^{1,1,3,4} C₁₇ H₁₅ Br F N O₃ S

SOURCE – Abbott.

REFERENCES

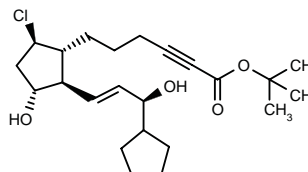
1. Carroll, W.A. et al. (Abbott Laboratories Inc.) *Potassium channel openers*. EP 1040097, US 6265417, WO 9931059.
2. Brune, M. et al. *Characterization of A-278637, a novel ATP-sensitive potassium channel (K_{ATP}) opener with potential for the treatment of bladder overactivity*. J Urol 2001, 165(5, Suppl.): Abst 150.
3. Carroll, W.A. et al. *In vitro and in vivo profile of A-278637, a novel bladder selective KATP channel opener*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MED1 195.
4. Drizin, I. et al. *Novel sulfonyldihydropyridine potassium channel openers with potential utility in the treatment of overactive bladder (OAB)*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MED1 197.

*Identified compound **278034** (see **278029**) Drug Data Rep 1999, 021(07): 0614.

TREATMENT OF RENAL DISEASES

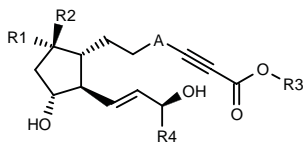
304359

9-Chloro-15-cyclopentyl-9-deoxy-3,3,4,4-tetradehydro-2,16,17,18,19,20-hexanorprostaglandin F_{1β} *tert*-butyl ester



C₂₃ H₃₅ Cl O₄; Mol wt: 410.9785

ACTION – A representative compound from a series of prostaglandin derivatives with PGD₂-like agonist activity, proven to increase cAMP production *in vitro* in bovine fetal trachea-derived cells. Potentially useful in the treatment of nephropathies, as well as cardiovascular disorders such as ischemic cardiopathy, hypertension and heart failure. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
304360	Cl	H	Me	cyclopentyl	-CH2-	C ₂₀ H ₂₉ ClO ₄
304361	Cl	H	H	cyclopentyl	-(CH2)2-	C ₂₀ H ₂₉ ClO ₄
304362	H	Cl	i-Pr	cyclohexyl	-(CH2)2-	C ₂₄ H ₃₇ ClO ₄
304363	H	Cl	Me	cyclohexyl	-(CH2)3-	C ₂₃ H ₃₅ ClO ₄
304364	H	Cl	H	cyclopentyl-CH2	-CH2-	C ₂₀ H ₂₉ ClO ₄
304365	H	Cl	Me	cyclohexyl-CH2	-CH2-	C ₂₂ H ₃₃ ClO ₄
304366	H	Cl	H	cyclohexyl-CH2	-(CH2)3-	C ₂₃ H ₃₅ ClO ₄
304367	H	Cl	Me	(R)-CH2CH(Me)-CH2CH2CH=C(Me)2	-(CH2)2-	C ₂₅ H ₃₉ ClO ₄
304368	H	Cl	H	(R)-CH(Me)CH2-ethynylene-Et	-(CH2)2-	C ₂₂ H ₃₁ ClO ₄

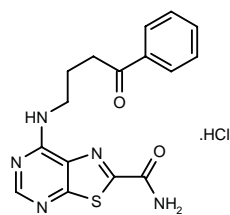
SOURCE – Taisho.

REFERENCES

1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin derivs.* JP 2001089443.

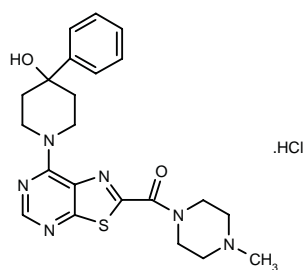
304947

7-(4-Oxo-4-phenylbutylamino)thiazolo[5,4-*d*]pyrimidine-2-carboxamide hydrochloride



C16 H15 N5 O2 S . HCl; Mol wt: 377.8544

ACTION – Agent for the treatment of nephropathy, cardiopathy, inflammatory, allergic and autoimmune disorders, arteriosclerosis, diabetic retinopathy, infection, cancer and transplant rejection, proven to inhibit T-cell proliferation and the production of IL-2 in murine anti-CD3 antibody-stimulated murine spleen T-cells (87 and 97% inhibition, respectively, at 17 μ M). *In vivo*, compound was effective against lipopolysaccharide (LPS)-induced mortality in mice, survival rate being 100 and 89% at 26 and 42 h, respectively, after LPS injection when given at 30 mg/kg i.p. Another condensed heterocyclic compound is:



304949: C22 H26 N6 O2 S . HCl

SOURCE – Takeda.

REFERENCES

1. Sugihara, Y. et al. (Takeda Chemical Industries, Ltd.) *Condensed heterocyclic cpds., their preparation method and use.* JP 2001097979.

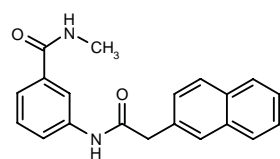
GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

BAS-118*

271508

N-Methyl-3-[2-(2-naphthyl)acetamido]benzamide



C20 H18 N2 O2; Mol wt: 318.3742

ACTION – Anti-*Helicobacter pylori* agent (MIC = 0.05 μ g/ml against clinically isolated *H. pylori* strain 31A) that is inactive against various strains of other bacteria and fungi at up to 1000 μ g/ml. Potentially useful for the treatment of gastric ulcers.

SOURCE – Mitsubishi Chemical.

REFERENCES

1. Ando, R. et al. (Mitsubishi Chemical Corp.) *Amide derivs.* EP 0887341, JP 1999071336.

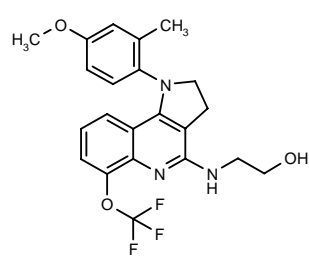
2. Ando, R. et al. 3-(Arylacetylamino)-N-methylbenzamides: New class of selective anti-*Helicobacter pylori* agents. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 248.

*Identified compound 271508 Drug Data Rep 1999, 021(02): 0141.

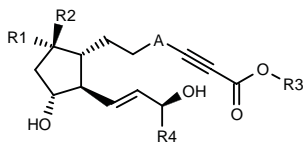
KR-60436

306490

2-[1-(4-Methoxy-2-methylphenyl)-6-(trifluoromethoxy)-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-ylamino]ethanol



C22 H22 F3 N3 O3; Mol wt: 433.4278



Compound	R1	R2	R3	R4	A	Formula
304360	Cl	H	Me	cyclopentyl	-CH2-	C ₂₀ H ₂₉ ClO ₄
304361	Cl	H	H	cyclopentyl	-(CH2)2-	C ₂₀ H ₂₉ ClO ₄
304362	H	Cl	i-Pr	cyclohexyl	-(CH2)2-	C ₂₄ H ₃₇ ClO ₄
304363	H	Cl	Me	cyclohexyl	-(CH2)3-	C ₂₃ H ₃₅ ClO ₄
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304365	H	Cl	Me	cyclohexyl-CH2	-CH2-	C ₂₂ H ₃₃ ClO ₄
304366	H	Cl	H	cyclohexyl-CH2	-(CH2)3-	C ₂₃ H ₃₅ ClO ₄
304367	H	Cl	Me	(R)-CH2CH(Me)-CH2CH2CH=C(Me)2	-(CH2)2-	C ₂₅ H ₃₉ ClO ₄
304368	H	Cl	H	(R)-CH(Me)CH2-ethynylene-Et	-(CH2)2-	C ₂₂ H ₃₁ ClO ₄

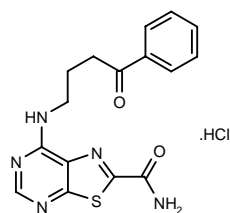
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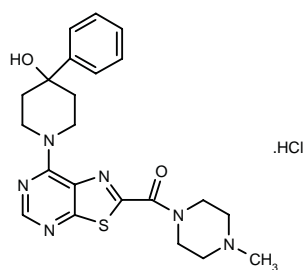
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7-(4-Oxo-4-phenylbutylamino)thiazolo[5,4-*d*]pyrimidine-2-carboxamide hydrochloride



C16 H15 N5 O2 S . HCl; Mol wt: 377.8544

ACTION – Agent for the treatment of nephropathy, cardiopathy, inflammatory, allergic and autoimmune disorders, arteriosclerosis, diabetic retinopathy, infection, cancer and transplant rejection, proven to inhibit T-cell proliferation and the production of IL-2 in murine anti-CD3 antibody-stimulated murine spleen T-cells (87 and 97% inhibition, respectively, at 17 μM). *In vivo*, compound was effective against lipopolysaccharide (LPS)-induced mortality in mice, survival rate being 100 and 89% at 26 and 42 h, respectively, after LPS injection when given at 30 mg/kg i.p. Another condensed heterocyclic compound is:



304949: C22 H26 N6 O2 S . HCl

SOURCE – Takeda.

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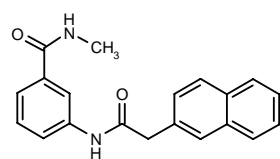
GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

BAS-118*

271508

N-Methyl-3-[2-(2-naphthyl)acetamido]benzamide



C20 H18 N2 O2; Mol wt: 318.3742

ACTION – Anti-*Helicobacter pylori* agent (MIC = 0.05 μg/ml against clinically isolated *H. pylori* strain 31A) that is inactive against various strains of other bacteria and fungi at up to 1000 μg/ml. Potentially useful for the treatment of gastric ulcers.

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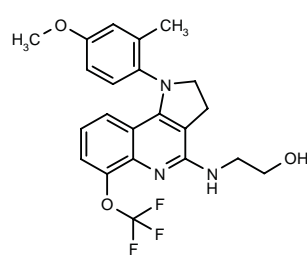
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*Identified compound 271508 Drug Data Rep 1999, 021(02): 0141.

KR-60436

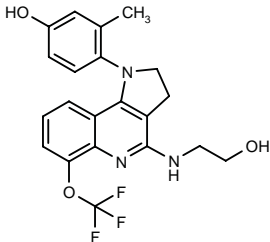
306490

2-[1-(4-Methoxy-2-methylphenyl)-6-(trifluoromethoxy)-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-ylamino]ethanol



C22 H22 F3 N3 O3; Mol wt: 433.4278

ACTION – Potential antiulcer agent, a reversible H⁺/K⁺-ATPase inhibitor proven to inhibit gastric acid secretion (ED₅₀ = 10 mg/kg) and to protect against ethanol-induced gastric lesions (ED₅₀ = 10 mg/kg) in rats. *In vitro* studies using rat and human liver microsomes showed that compound is extensively metabolized to at least 7 metabolites, among which **O-demethyl-KR-60436** showed similar proton pump-inhibitory activity to the parent compound.



O-Demethyl-KR-60436 [306491]: C21 H20 F3 N3 O3

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

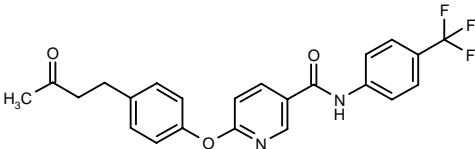
REFERENCES

1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *Pyrolo[3,2-c]-quinoline derivs. containing haloalkoxy group and pharmaceutically acceptable salts thereof*. CA 2268166, EP 0966466, JP 2000504352, US 6011044, WO 9909029.
2. Lee, H.M. et al. *High performance liquid chromatographic analysis of a new proton pump inhibitor KR60436 and its active metabolite O-demethyl-KR60436 in rat plasma samples using column-switching*. Arch Pharmacol Res 2001, 24(3): 207.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

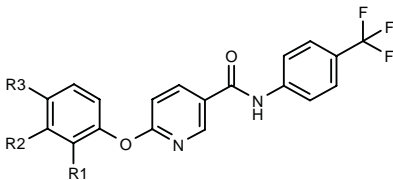
304265

6-[4-(3-Oxobutyl)phenoxy]-N-[4-(trifluoromethyl)phenyl]-pyridine-3-carboxamide



C23 H19 F3 N2 O3; Mol wt: 428.4081

ACTION – An inhibitor of the production of collagen (IC₅₀ = 0.15 μM), potentially useful for the treatment of diseases such as hepatic fibrosis and hepatic cirrhosis, pulmonary fibrosis, adult respiratory distress syndrome, dermatopathy, atherosclerosis, ocular diseases such as diabetic retinopathy and glaucoma, nephropathy, glomerulonephritis, and cartilage and bone diseases such as rheumatoid arthritis and osteoarthritis. Within this series of substituted pyridine derivatives, the following compounds are also included:



Compound	R1	R2	R3	Formula
304266	-CH2CH2CO-		H	C ₂₂ H ₁₅ F ₃ N ₂ O ₃
304267	H	H	Ac	C ₂₁ H ₁₅ F ₃ N ₂ O ₃

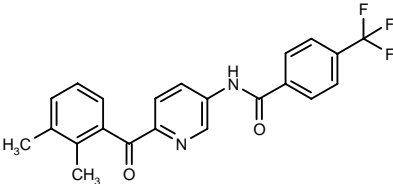
SOURCE – Otsuka.

REFERENCES

1. Edamatsu, H. et al. (Otsuka Pharmaceutical Co., Ltd.) *Pharmaceutical compsns. containing pyridine derivs.* JP 2001089450.

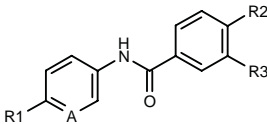
304342

N-[6-(2,3-Dimethylbenzoyl)pyridin-3-yl]-4-(trifluoromethyl)benzamide



C22 H17 F3 N2 O2; Mol wt: 398.3823

ACTION – An inhibitor of the production of collagen (IC₅₀ = 1.76 μM), potentially useful for the treatment of diseases such as hepatic fibrosis and hepatic cirrhosis, pulmonary fibrosis, adult respiratory distress syndrome, dermatopathy, atherosclerosis, ocular diseases such as diabetic retinopathy and glaucoma, nephropathy, glomerulonephritis, and cartilage and bone diseases such as rheumatoid arthritis and osteoarthritis. Other exemplified compounds from this series of substituted benzene derivatives include the following:



Compound	R1	R2	R3	A	Formula
304343	5-oxo-5,6,7,8-tetrahydro-1-Naph-O	Cl	Cl	CH	C ₂₃ H ₁₇ Cl ₂ NO ₃
304344	1-oxo-4-indanyl-O	Cl	Cl	CH	C ₂₂ H ₁₅ Cl ₂ NO ₃
304345	Cl	4-Ac-PhO	H	C(Cl)	C ₂₁ H ₁₅ Cl ₂ NO ₃
304346	CF3	4-Ac-PhO	H	CH	C ₂₂ H ₁₆ F ₃ NO ₃
304348	2,3-(Me)2-PhCO	Cl	Cl	N	C ₂₁ H ₁₆ Cl ₂ N ₂ O ₂

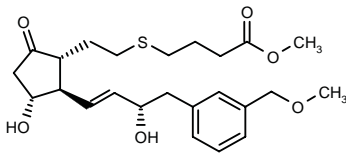
SOURCE – Otsuka.

REFERENCES

1. Kojima, Y. et al. (Otsuka Pharmaceutical Co., Ltd.) *Benzene derivs. or their pharmaceutically acceptable salts.* JP 2001089412.

307098

11 α ,15 α -Dihydroxy-16-(3-methoxymethylphenyl)-9-oxo-17,18,19,20-tetranor-5-thia-13(*E*)-prostenoic acid methyl ester



C24 H34 O6 S; Mol wt: 450.5926

ACTION – Methyl ester prodrug of a potent and selective prostanoid EP₄ receptor agonist (EC₅₀ = 1.6 nM) with subnanomolar affinity for mouse EP₄ receptors (K_i = 0.7 nM) and selectivity over mouse EP₁, EP₂ and EP₃ receptors (K_i > 10,000, 620 and 56 nM, respectively). *In vivo*, doses of 30-300 ng/kg/min i.v. significantly suppressed endotoxin-induced TNF- α production and increased plasma levels of IL-10. Moreover, compound (30 and 100 μ g/kg s.c.) improved indices of hepatitis induced by *Propionibacterium acnes*/endotoxin or galactosamine/endotoxin. Currently in phase I clinical trials.

SOURCE – Ono.

REFERENCES

1. Maruyama, T. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *5-Thia- ω -subst. phenyl-prostaglandin E derivs., process for producing the same and drugs containing the same as the active ingredient*. EP 1097922, JP 2001089444, WO 0003980.

2. Maruyama, T. and Tanaka, M. (Ono Pharmaceutical Co., Ltd.) *Remedies for diseases in association with decrease in bone mass*. WO 0137877.

3. Narita, M. and Yoshida, K. (Ono Pharmaceutical Co., Ltd.) *Erection insufficiency remedies*. WO 0124800.

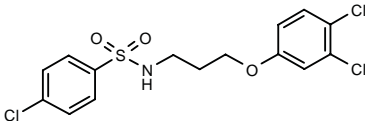
4. Maruyama, T. et al. *Design and synthesis of a highly selective EP4-receptor agonist. Part 2: 5-Thia and 9 β -haloPG derivatives with improved stability*. Bioorg Med Chem Lett 2001, 11(15): 2033.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

303723

4-Chloro-*N*-[3-(3,4-dichlorophenoxy)propyl]benzene-sulfonamide



C15 H14 Cl3 N O3 S; Mol wt: 394.7046

ACTION – Antidiabetic agent proven to significantly improve glucose tolerance and enhance insulin secretion when given to KKA γ mice at 80 mg/kg/day s.c. x 7 days before an oral glucose tolerance test.

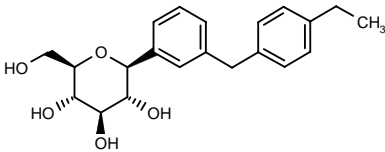
SOURCE – Shionogi.

REFERENCES

1. Yano, T. et al. (Shionogi & Co. Ltd.) *Preventive or therapeutic drugs for diabetes*. WO 0124786.

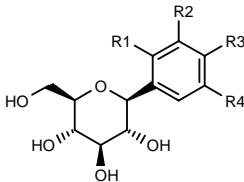
303770

1-Deoxy-1-[3-(4-ethylbenzyl)phenyl]- β -D-glucopyranose



C21 H26 O5; Mol wt: 358.4314

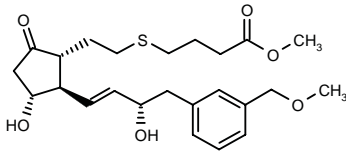
ACTION – An inhibitor of the sodium-dependent glucose transporter SGLT2, potentially useful for treating or delaying the progression or onset of diabetes, especially type 2 diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated plasma fatty acid or glycerol levels, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, diabetic complications, atherosclerosis and hypertension, as well as for increasing HDL cholesterol levels. Other specifically claimed compounds from this series of *C*-aryl glucosides are:



Compound	R1	R2	R3	R4	Formula
303777	H	H	H	4-MeO-PhCH2	C ₂₀ H ₂₄ O ₆
303778	H	H	H	4-(CF3O)-PhCH2	C ₂₀ H ₂₁ F ₃ O ₆
303779	H	H	H	4-MeS-PhCH2	C ₂₀ H ₂₄ O ₅ S
303781	OH	4-Me-PhCH2	H	H	C ₂₀ H ₂₄ O ₆
303782	H	H	H	4-Ac-PhCH2	C ₂₁ H ₂₄ O ₆
303783	H	H	H	4-[MeCH(OH)]-PhCH2	C ₂₁ H ₂₆ O ₆
303785	H	H	Me	4-MeO-PhCH2	C ₂₁ H ₂₆ O ₆
303786	H	H	Me	4-(OCHF2)-PhCH2	C ₂₁ H ₂₄ F ₂ O ₆
303787	H	H	Me	4-MeS-PhCH2	C ₂₁ H ₂₆ O ₅ S
303788	H	H	Cl	4-MeS-PhCH2	C ₂₀ H ₂₃ ClO ₅ S
303789	H	H	Cl	4-MeO-PhCH2	C ₂₀ H ₂₃ ClO ₆
303790	H	H	OMe	4-Et-PhCH2	C ₂₂ H ₂₈ O ₆
303791	OH	CONHEt	OH	4-MeO-PhCH2	C ₂₃ H ₂₉ NO ₉
303792	H	H	H	4-Me-Ph	C ₁₉ H ₂₂ O ₅

307098

11 α ,15 α -Dihydroxy-16-(3-methoxymethylphenyl)-9-oxo-17,18,19,20-tetranor-5-thia-13(*E*)-prostenoic acid methyl ester



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SOURCE – Ono.

REFERENCES

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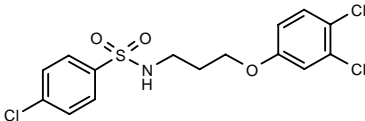
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

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4-Chloro-*N*-[3-(3,4-dichlorophenoxy)propyl]benzene-sulfonamide



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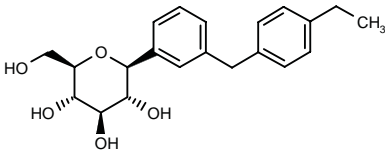
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1. Yano, T. et al. (Shionogi & Co. Ltd.) *Preventive or therapeutic drugs for diabetes*. WO 0124786.

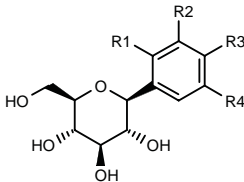
303770

1-Deoxy-1-[3-(4-ethylbenzyl)phenyl]- β -D-glucopyranose



C21 H26 O5; Mol wt: 358.4314

ACTION – An inhibitor of the sodium-dependent glucose transporter SGLT2, potentially useful for treating or delaying the progression or onset of diabetes, especially type 2 diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated plasma fatty acid or glycerol levels, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, diabetic complications, atherosclerosis and hypertension, as well as for increasing HDL cholesterol levels. Other specifically claimed compounds from this series of *C*-aryl glucosides are:



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303778	H	H	H	4-(CF3O)-PhCH2	C ₂₀ H ₂₁ F ₃ O ₆
303779	H	H	H	4-MeS-PhCH2	C ₂₀ H ₂₄ O ₅ S
303781	OH	4-Me-PhCH2	H	H	C ₂₀ H ₂₄ O ₆
303782	H	H	H	4-Ac-PhCH2	C ₂₁ H ₂₄ O ₆
303783	H	H	H	4-[MeCH(OH)]-PhCH2	C ₂₁ H ₂₆ O ₆
303785	H	H	Me	4-MeO-PhCH2	C ₂₁ H ₂₆ O ₆
303786	H	H	Me	4-(OCHF2)-PhCH2	C ₂₁ H ₂₄ F ₂ O ₆
303787	H	H	Me	4-MeS-PhCH2	C ₂₁ H ₂₆ O ₅ S
303788	H	H	Cl	4-MeS-PhCH2	C ₂₀ H ₂₃ ClO ₅ S
303789	H	H	Cl	4-MeO-PhCH2	C ₂₀ H ₂₃ ClO ₆
303790	H	H	OMe	4-Et-PhCH2	C ₂₂ H ₂₈ O ₆
303791	OH	CONHEt	OH	4-MeO-PhCH2	C ₂₃ H ₂₉ NO ₉
303792	H	H	H	4-Me-Ph	C ₁₉ H ₂₂ O ₅

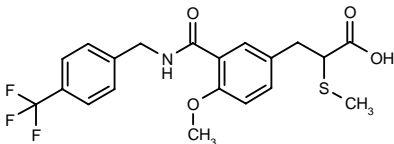
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Ellsworth, B. et al. (Bristol-Myers Squibb Co.) *C-Aryl glucoside SGLT2 inhibitors*. WO 0127128.

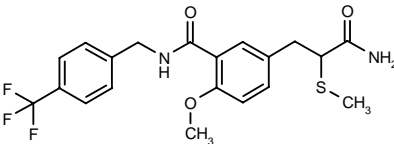
303998

3-[4-Methoxy-3-[*N*-[4-(trifluoromethyl)benzyl]-carbamoyl]phenyl]-2-(methylsulfanyl)propionic acid



C20 H20 F3 N O4 S; Mol wt: 427.4410

ACTION – Agent for the treatment or prevention of hyperlipidemia and diabetes, a human peroxisome proliferator-activated receptor (PPAR) agonist. *In vitro*, compound exhibited transcriptional activation of human PPAR α in a luciferase reporter gene assay using CHO cells expressing the human receptor (EC_{50} = 1.2 μ M vs. 1.3 μ M for [8*S*]-HETE). Another compound from this series of *o*-anisamide derivatives is:



303999: C20 H21 F3 N2 O3 S

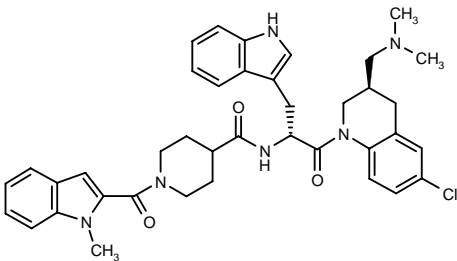
SOURCE – Kyorin.

REFERENCES

1. Satoh, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *O-Anisamide derivs*. WO 0121578.

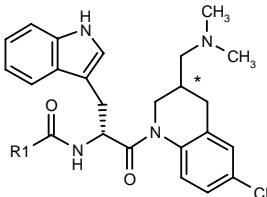
304045

N-[2-[6-Chloro-3(*R*)-(dimethylaminomethyl)-1,2,3,4-tetrahydroquinolin-1-yl]-1(*R*)-(1*H*-indol-3-ylmethyl)-2-oxoethyl]-1-(1-methyl-1*H*-indol-2-ylcarbonyl)piperidine-4-carboxamide



C39 H43 Cl N6 O3; Mol wt: 679.2607

ACTION – Somatostatin receptor modulator with selectivity for the sst₂ subtype relative to other subtypes, as demonstrated in binding assays (IC_{50} = 0.3 nM; IC_{50} sst₃ and sst₅ = 80 and 400 nM, respectively). Potentially useful for the treatment or prevention of diabetes, diabetic nephropathy, cancer and chronic diarrhea. Other compounds within this series of amine derivatives include the following:



Compound	R1	* Isomer	Formula
304046	1-(2-indolyl-CO)-4-Pip	R,S	C ₃₈ H ₄₁ ClN ₆ O ₃
304047	1-(PhCO)-4-Pip-CH ₂ CH ₂	R	C ₃₈ H ₄₄ ClN ₅ O ₃
304048	4-(4-Cl-PhCO)-1-Pip	R	C ₃₆ H ₃₉ Cl ₂ N ₅ O ₃
304049	4-(PhO)-1-Pip	R	C ₃₅ H ₄₀ ClN ₅ O ₃

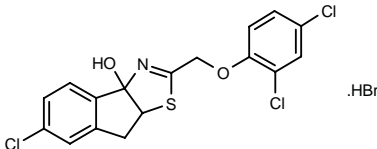
SOURCE – Takeda.

REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *Amine derivs*. WO 0125228.

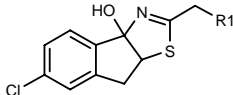
304748

6-Chloro-2-(2,4-dichlorophenoxyethyl)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]thiazol-3a-ol hydrobromide



C17 H12 Cl3 N O2 S . HBr; Mol wt: 481.6237

ACTION – Agent for the treatment or prevention of obesity and type 2 diabetes, proven to decrease condensed milk consumption by 95% in fasted mice pretreated with 50 mg/kg p.o. Other compounds from this series of indeno-, naphtho- and benzocyclohepta-dihydrothiazole derivatives include the following:



Compound	R1	Formula
304749	OPh	C ₁₇ H ₁₄ ClNO ₂ S
304750	4-MeO-PhO	C ₁₈ H ₁₆ ClNO ₃ S
304751	2-Cl-PhO	C ₁₇ H ₁₃ Cl ₂ NO ₂ S
304752	4-Cl-PhO	C ₁₇ H ₁₃ Cl ₂ NO ₂ S
304753	3,5-(Cl)2-PhO	C ₁₇ H ₁₂ Cl ₃ NO ₂ S
304754	4-t-Bu-PhO	C ₂₁ H ₂₂ ClNO ₂ S
304755	OCH ₂ CH ₂ Ph	C ₁₉ H ₁₈ ClNO ₂ S
304756	OC ₆ H ₁₃	C ₁₇ H ₂₂ ClNO ₂ S
304757	SCH ₂ Ph	C ₁₈ H ₁₆ ClNOS ₂

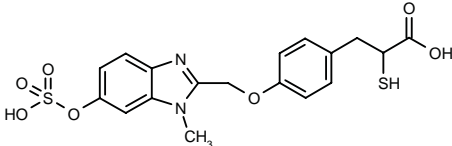
SOURCE – Aventis Pharma.

REFERENCES

1. Jaehne, G. et al. (Aventis Pharma Deutschland GmbH) *Indeno-, naphtho-, and benzocyclohepta-dihydrothiazole derivs., the production thereof and their use as anorectic medicaments*. WO 0132638.

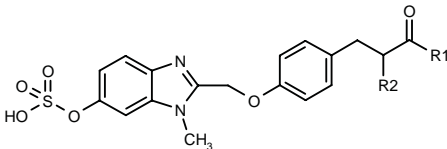
304979

3-[4-[1-Methyl-6-(sulfooxy)-1*H*-benzimidazol-2-yl]methoxy]phenyl]-2-sulfanylpropionic acid



C18 H18 N2 O7 S2; Mol wt: 438.4792

ACTION – Agent with blood sugar-lowering properties that is potentially useful for the treatment of diabetes, hyperlipidemia, obesity, hypertension, diabetic complications and cardiovascular diseases, among others. Other exemplified sulfoxybenzimidazole derivatives include the following:



Compound	R1	R2	Formula
304980	OH	SC5H11	C ₂₃ H ₂₈ N ₂ O ₇ S ₂
304981	OH	i-BuSO	C ₂₂ H ₂₆ N ₂ O ₆ S ₂
304982	OH	SO2Pr	C ₂₁ H ₂₄ N ₂ O ₆ S ₂
304983	OH	SO2C(Me)2Et	C ₂₃ H ₂₈ N ₂ O ₆ S ₂
304984	NH2	SMe	C ₁₉ H ₂₁ N ₃ O ₆ S ₂
304985	NH2	cyclopentyl-S	C ₂₃ H ₂₇ N ₃ O ₆ S ₂
304987	NH2	SOCH(Me)Et	C ₂₂ H ₂₇ N ₃ O ₇ S ₂
304988	NH2	i-PrSO2	C ₂₁ H ₂₅ N ₃ O ₆ S ₂
304989	NH2	i-BuCH2SO2	C ₂₃ H ₂₉ N ₃ O ₆ S ₂

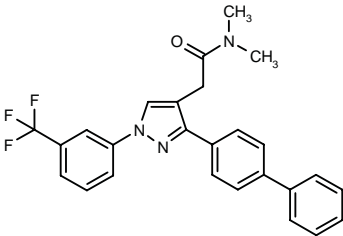
SOURCE – Sankyo.

REFERENCES

1. Iwabuchi, H. et al. (Sankyo Co., Ltd.) *Sulfoxybenzimidazole derivs*. JP 2001097954.

305862

2-[3-(Biphenyl-4-yl)-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]-*N,N*-dimethylacetamide



C26 H22 F3 N3 O; Mol wt: 449.4738

ACTION – Potent glucose-lowering agent (ED₅₀ = 3.0 mg/kg/day p.o. in *ob/ob* mice), also proven to significantly reduce insulin levels, consistent with an improvement in overall insulin sensitivity. Compound showed a favorable pharmacokinetic profile, with good oral bioavailability and a long duration of action in rats. It acts by a mechanism of action different from thiazolidinediones, as it did not activate the peroxisome proliferator-activated receptor PPAR γ . Potentially useful for the treatment of type 2 diabetes.

SOURCE – Novartis.

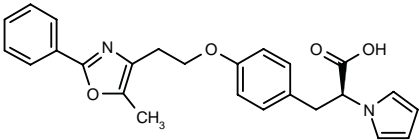
REFERENCES

1. Bebernitz, G.R. et al. *The effect of 1,3-diaryl-[1H]-pyrazole-4-acetamides on glucose utilization in ob/ob mice*. J Med Chem 2001, 44(16): 2601.

GW-7282

307365

3-[4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]-2(*S*)-(1-pyrrolyl)propionic acid



C25 H24 N2 O4; Mol wt: 416.4746

ACTION – Tyrosine-based peroxisome proliferator-activated receptor PPAR γ agonist, potentially useful for the treatment of type 2 diabetes.

SOURCE – GlaxoSmithKline.

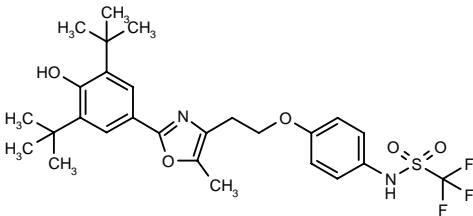
REFERENCES

1. Liu, K.G. et al. *Structure-based design and synthesis of tyrosine-based PPAR γ agonists*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 168.

KT6-207

307374

N-[4-[2-[2-[3,5-Bis(*tert*-butyl)-4-hydroxyphenyl]-5-methyl-oxazol-4-yl]ethoxy]phenyl]-1,1,1-trifluoromethanesulfonamide



C27 H33 F3 N2 O5 S; Mol wt: 554.6267

ACTION – Nonthiazolidinedione compound with peroxisome proliferator-activated receptor PPAR γ - and PPAR α -agonist activity (EC_{50} = 2.1 and 24.7 nM, respectively, in transactivation assays). In diabetic *db/db* mice, compound (1 and 3 mg/kg/day p.o. for 14 days) exhibited dose-dependent hypoglycemic (21 and 36% reduction, respectively) and hypolipidemic activity (47 and 69% reduction, respectively). It also exhibited antioxidant activity *in vitro* in both rat brain homogenates and human plasma LDL (IC_{50} = 1.2 and 4.9 μ M, respectively), and it showed metabolic stability in human liver microsomes. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Kotobuki.

REFERENCES

1. Toyama, T. et al. (Kotobuki Pharmaceutical Co., Ltd.) *Ether o amide derivs., their preparation method and therapeutic agent for diabetes containing them.* JP 2001261662.

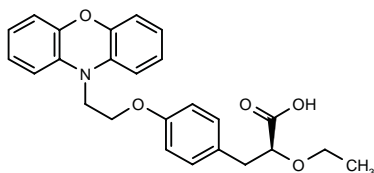
2. Tomiyama, H. et al. *Non-thiazolidinedione PPAR γ - and α -dual agonists for the treatment of type II diabetes mellitus.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 38.

NN-622

275437

2(S)-Ethoxy-3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-propionic acid

(-)-DRF-2725
NNC-61-0029



C₂₅ H₂₅ N O₅; Mol wt: 419.4745

White solid, m.p. 89-90 °C; $[\alpha]_D -12.6^\circ$ (1%, CHCl₃).

ACTION – Antidiabetic agent, a dual peroxisome proliferator-activated receptor PPAR γ /PPAR α agonist with potent hypoglycemic and lipid-modulating activity. In *db/db* mice, compound produced a 56% reduction in plasma glucose and a 62% reduction in triglycerides at a dose of 1 mg/kg p.o. x 9 days, and in diabetic and prediabetic ZDF rats, it improved the histological appearance and function of β -cells. In insulin-resistant high-fat-fed rats, a dose of 3 mg/kg/day for 2 weeks significantly reduced plasma triglycerides, insulin, leptin and muscle lipids, with an efficacy comparable to rosiglitazone. Unlike rosiglitazone, compound did not cause hepatomegaly and produced additional beneficial effects on liver triglycerides, visceral fat and hepatic glucose output during hyperinsulinemia. Pharmacokinetic studies in healthy volunteers showed rapid absorption and slow elimination, with a mean t_{max} of 1.4-2.5 h and a mean elimination half-life of 68-97 h. In a multiple-dose, double-blind, placebo-controlled trial in healthy subjects and patients with type 2 diabetes, compound showed a very similar pharmacokinetic profile in healthy and diabetic subjects, with a plasma elimination half-lives of 104 h in healthy subjects and 122 h in diabetic patients.

SOURCES – Dr. Reddy's Research Foundation; Novo Nordisk.

REFERENCES

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2. Lohray, B.B. et al. (Dr. Reddy's Research Foundation) *Novel tricyclic cpds. and their use in medicine; process for their preparation and pharmaceutical compsn. containing them.* EP 1049684, WO 9919313.

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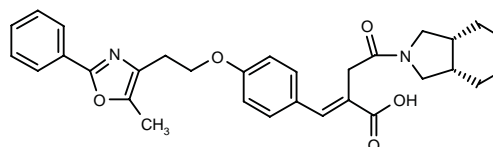
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Y-39677

296303

cis-2-[2-(Octahydro-2*H*-isoindol-2-yl)-2-oxoethyl]-3-[4-[2-(5-methyl-2-phenylloxazol-4-yl)ethoxy]phenyl]-2(*E*)-propenoic acid



C₃₁ H₃₄ N₂ O₅; Mol wt: 514.6186

ACTION – Dual insulin sensitizer and insulin-releasing agent proven to significantly stimulate insulin release in HIT-T15 cells with greater efficacy than nateglinide, and to produce triglyceride accumulation in 3T3-L1 cells with a similar profile to pioglitazone. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Welfide.

REFERENCES

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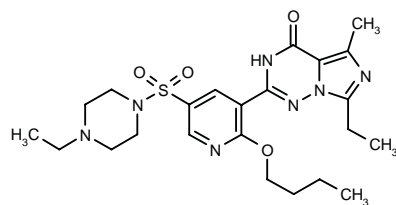
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TREATMENT OF MALE SEXUAL DYSFUNCTION

303593

2-[2-Butoxy-5-(4-ethylpiperazin-1-ylsulfonyl)pyridin-3-yl]-7-ethyl-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one



C23 H33 N7 O4 S; Mol wt: 505.6405

ACTION – Potent and selective inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ < 100 nM), with potential for the treatment of PDE5-mediated disorders or conditions, particularly male erectile dysfunction and female sexual dysfunction. A representative compound from a series of imidazo[5,1-f][1,2,4]triazine derivatives.

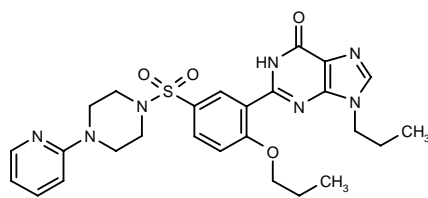
SOURCE – Pfizer.

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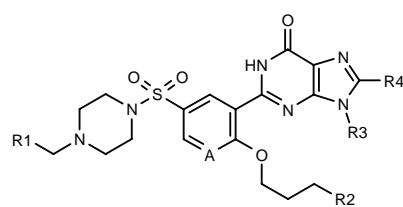
303595

2-[2-Propoxy-5-[4-(2-pyridyl)piperazin-1-ylsulfonyl]-phenyl]-9-propylhypoxanthine



C26 H31 N7 O4 S; Mol wt: 537.6419

ACTION – Potent and selective inhibitor of phosphodiesterase type 5 (PDE5; 100% inhibition at 10 nM), with potential for the treatment of PDE5-mediated disorders or conditions, particularly male erectile dysfunction and female sexual dysfunction. Other exemplified compounds from this series of 2-(2-alkoxy-5-heterocyclisulfonyl-phenyl)purin-6-ones include the following:



Compound	R1	R2	R3	R4	A	Formula
303596	Me	H	H	H	CH	C ₂₀ H ₂₆ N ₆ O ₄ S
303600	Me	H	4-NH2-Ph	H	CH	C ₂₆ H ₃₁ N ₇ O ₄ S
303601	H	H	H	3-Pyr	CH	C ₂₄ H ₂₇ N ₇ O ₄ S
303602	Me	Me	Pr	CH2Ph	N	C ₃₀ H ₃₉ N ₇ O ₄ S

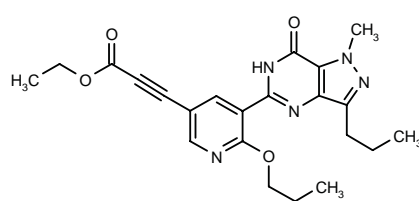
SOURCE – Pfizer.

REFERENCES

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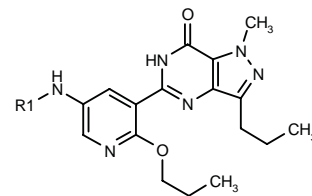
303745

3-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6-propoxypyridin-3-yl]-2-propynoic acid ethyl ester



C22 H25 N5 O4; Mol wt: 423.4705

ACTION – An inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 0.3 nM), with potential for the treatment of male erectile dysfunction, impotence and female sexual dysfunction. Other exemplified compounds from this series of dihydropyrazolo[4,3-d]pyrimidin-7-ones include the following:



Compound	R1	Formula
303746	SO2Me	C ₁₈ H ₂₄ N ₆ O ₄ S
303747	COCH2CO2Me	C ₂₁ H ₂₆ N ₆ O ₅
303748	SO2CH2CO2H	C ₁₉ H ₂₄ N ₆ O ₆ S

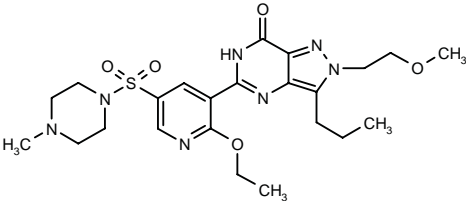
SOURCE – Pfizer.

REFERENCES

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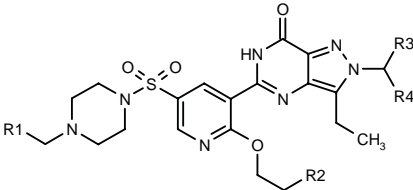
303749

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)pyridin-3-yl]-2-(2-methoxyethyl)-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one



C23 H33 N7 O5 S; Mol wt: 519.6237

ACTION – An inhibitor of phosphodiesterase type 5 (PDE5), with potential for the treatment of male erectile dysfunction, impotence and female sexual dysfunction. Other specifically claimed compounds from this series of dihydropyrazolo[4,3-*d*]pyrimidin-7-ones include the following:



Compound	R1	R2	R3	R4	Formula
303750	Me	H	CH2NHMe	H	C ₂₃ H ₃₄ N ₈ O ₄ S
303751	Me	Et	-CH2N(Me)CH2-		C ₂₆ H ₃₈ N ₈ O ₄ S
303752	Me	OMe	Et	Me	C ₂₆ H ₃₇ N ₇ O ₅ S
303753	H	OMe	cyclobutyl	H	C ₂₅ H ₃₅ N ₇ O ₅ S
303754	Me	OMe	Et	(S)-Me	C ₂₅ H ₃₇ N ₇ O ₅ S

SOURCE – Pfizer.

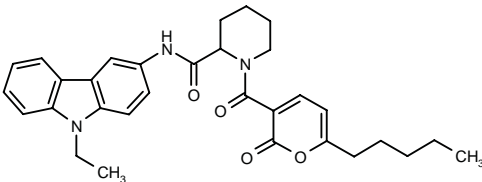
REFERENCES

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AGENTS FOR FEMALE INFERTILITY

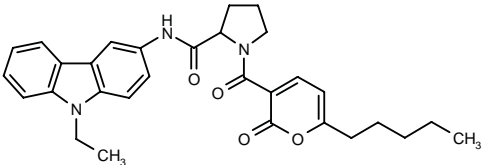
304667

N-(9-Ethyl-9*H*-carbazol-3-yl)-1-(2-oxo-6-pentyl-2*H*-pyran-3-ylcarbonyl)piperidine-2-carboxamide



C31 H35 N3 O4; Mol wt: 513.6345

ACTION – Agent for the treatment of infertility, a follicle-stimulating hormone (FSH) agonist, as demonstrated in a luciferase reporter gene assay using CHO cells stably expressing human FSH receptors (EC₅₀ = 3.9 nM vs. 1.47 pM for FSH). In addition, compound was shown to increase estradiol production in a rat granulosa cell assay (EC₅₀ = 1.2 μM). Another specifically claimed compound from this series of tetrahydroisoquinolinecarboxamides, piperidinecarboxamides, pyrrolidinecarboxamides and 2-amino-3-pyridinecarboxamides is:



304668: C30 H33 N3 O4

SOURCE – Applied Research Systems.

REFERENCES

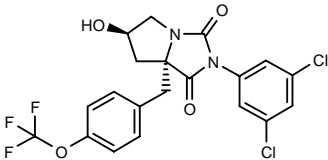
1. El Tayer, N. et al. (Applied Research Systems ARS Holdings NV) *FSH mimetics for the treatment of infertility.* EP 1102763, US 6235755, WO 0008015.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

304569

2-(3,5-Dichlorophenyl)-6(*R*)-hydroxy-7a(*R*)-[4-(trifluoromethoxy)benzyl]perhydropyrrolo[1,2-*c*]imidazole-1,3-dione



C20 H15 Cl2 F3 N2 O4; Mol wt: 475.2485

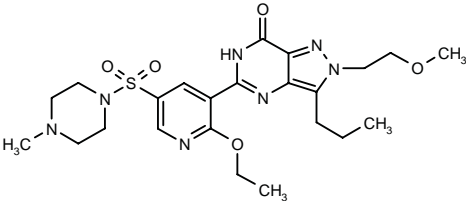
SOURCE – Pfizer.

REFERENCES

1. Allerton, C.M.N. et al. (Pfizer Ltd.;Pfizer Inc.) 5-(2-Substd.-5-heterocycl-yl-sulphonylpyrid-3-yl)-dihydropyrazolo[4,3-d]pyrimidin-7-ones as phosphodiesterase inhibitors. WO 0127112.

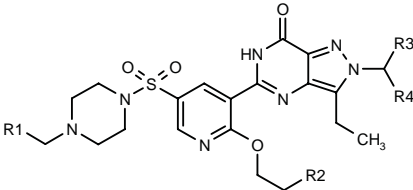
303749

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)pyridin-3-yl]-2-(2-methoxyethyl)-3-propyl-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-7-one



C23 H33 N7 O5 S; Mol wt: 519.6237

ACTION – An inhibitor of phosphodiesterase type 5 (PDE5), with potential for the treatment of male erectile dysfunction, impotence and female sexual dysfunction. Other specifically claimed compounds from this series of dihydropyrazolo[4,3-d]pyrimidin-7-ones include the following:



Compound	R1	R2	R3	R4	Formula
303750	Me	H	CH2NHMe	H	C ₂₃ H ₃₄ N ₈ O ₄ S
303751	Me	Et	-CH2N(Me)CH2-		C ₂₆ H ₃₈ N ₈ O ₄ S
303752	Me	OMe	Et	Me	C ₂₆ H ₃₇ N ₇ O ₅ S
303753	H	OMe	cyclobutyl	H	C ₂₅ H ₃₅ N ₇ O ₅ S
303754	Me	OMe	Et	(S)-Me	C ₂₅ H ₃₇ N ₇ O ₅ S

SOURCE – Pfizer.

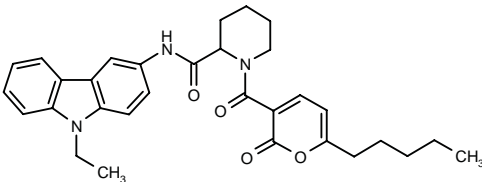
REFERENCES

1. Bunnage, M.E. et al. (Pfizer Ltd.;Pfizer Inc.) *Pharmaceutically active cpds.* WO 0127113.

AGENTS FOR FEMALE INFERTILITY

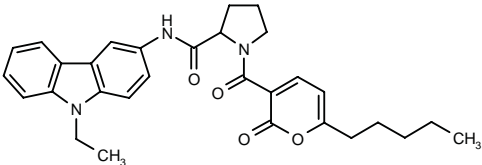
304667

N-(9-Ethyl-9H-carbazol-3-yl)-1-(2-oxo-6-pentyl-2H-pyran-3-ylcarbonyl)piperidine-2-carboxamide



C31 H35 N3 O4; Mol wt: 513.6345

ACTION – Agent for the treatment of infertility, a follicle-stimulating hormone (FSH) agonist, as demonstrated in a luciferase reporter gene assay using CHO cells stably expressing human FSH receptors (EC₅₀ = 3.9 nM vs. 1.47 pM for FSH). In addition, compound was shown to increase estradiol production in a rat granulosa cell assay (EC₅₀ = 1.2 μM). Another specifically claimed compound from this series of tetrahydroisoquinolinecarboxamides, piperidinecarboxamides, pyrrolidinecarboxamides and 2-amino-3-pyridinecarboxamides is:



304668: C30 H33 N3 O4

SOURCE – Applied Research Systems.

REFERENCES

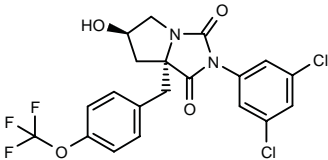
1. El Tayer, N. et al. (Applied Research Systems ARS Holdings NV) *FSH mimetics for the treatment of infertility.* EP 1102763, US 6235755, WO 0008015.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

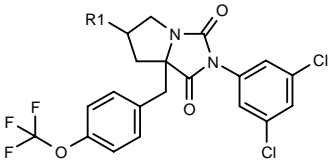
304569

2-(3,5-Dichlorophenyl)-6(R)-hydroxy-7a(R)-[4-(trifluoromethoxy)benzyl]perhydropyrrolo[1,2-c]imidazole-1,3-dione



C20 H15 Cl2 F3 N2 O4; Mol wt: 475.2485

ACTION – An inhibitor of $\alpha_L\beta_2$ integrin (LFA-1, CD11a/CD18)-mediated cell adhesion, potentially useful for the treatment of a broad range of disorders including psoriasis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, atopic dermatitis, Sjögren's syndrome, transplant rejection and graft-versus-host disease. Other specifically claimed nitrogen-containing bicyclic compounds are:



Compound	R1	Isomer	Formula
304570	NHAc	6S,7aR	C ₂₂ H ₁₈ Cl ₂ F ₃ N ₃ O ₄
304571	NHCOCH ₂ CH ₂ CONH ₂	6S,7aR	C ₂₄ H ₂₁ Cl ₂ F ₃ N ₄ O ₅
304572	4-Me-1-Piz-COCH ₂ CH ₂ CONH	6S,7aR	C ₂₉ H ₃₀ Cl ₂ F ₃ N ₅ O ₅
304573	3-Pyr-CONH	6S,7aR	C ₂₆ H ₁₉ Cl ₂ F ₃ N ₄ O ₄
304574	1-pyrrolidinyl-CONH	6S,7aR	C ₂₅ H ₂₃ Cl ₂ F ₃ N ₄ O ₄
304575	CONH ₂	6R,7aR	C ₂₁ H ₁₆ Cl ₂ F ₃ N ₃ O ₄
304576	4-morpholinyl-CO	6R,7aR	C ₂₅ H ₂₂ Cl ₂ F ₃ N ₃ O ₅
304577	CON(Me) ₂	6R,7aR	C ₂₃ H ₂₀ Cl ₂ F ₃ N ₃ O ₄
304578	CONHMe	6R,7aR	C ₂₂ H ₁₈ Cl ₂ F ₃ N ₃ O ₄
304621	4-morpholinyl-NHCO	6R,7aR	C ₂₅ H ₂₃ Cl ₂ F ₃ N ₄ O ₅

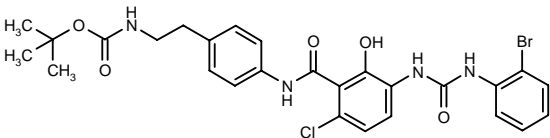
SOURCE – Tanabe Seiyaku.

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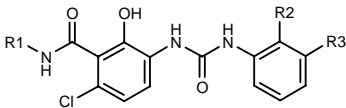
304991

N-[2-[4-[3-[3-(2-Bromophenyl)ureido]-6-chloro-2-hydroxy-benzamido]phenyl]ethyl]carbamic acid *tert*-butyl ester



C₂₇ H₂₈ Br Cl N₄ O₅; Mol wt: 603.8982

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist expected to be useful in the treatment of disorders characterized by excessive or unregulated IL-8, i.e., psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft-vs.-host disease, Alzheimer's disease, allograft rejection, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cell release, among others. Other specifically claimed diphenyl urea compounds are:



Compound	R1	R2	R3	Formula
304993	4-(t-BuOCONHCH ₂ CH ₂)-Ph	Cl	Cl	C ₂₇ H ₂₇ Cl ₃ N ₄ O ₅
304994	4-(NH ₂ CH ₂ CH ₂)-Ph	Br	H	C ₂₂ H ₂₀ BrClN ₄ O ₃
304995	4-(NH ₂ CH ₂ CH ₂)-Ph	Cl	Cl	C ₂₂ H ₁₉ Cl ₃ N ₄ O ₃
304996	t-BuOCONH(CH ₂) ₆	Cl	Cl	C ₂₅ H ₃₁ Cl ₃ N ₄ O ₅
304997	t-BuOCONH(CH ₂) ₆	Br	H	C ₂₅ H ₃₂ BrClN ₄ O ₅
304999	(CH ₂) ₆ NH ₂	Cl	Cl	C ₂₀ H ₂₃ Cl ₃ N ₄ O ₃
305000	(CH ₂) ₆ NH ₂	Br	H	C ₂₀ H ₂₄ BrClN ₄ O ₃

SOURCE – GlaxoSmithKline.

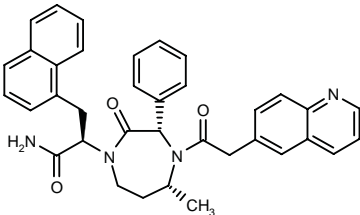
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TOPICAL ANTIINFLAMMATORY AGENTS

303744

2(*R*)-[5(*R*)-Methyl-2-oxo-3(*S*)-phenyl-4-[2-(6-quinoliny)-acetyl]perhydro-1,4-diazepin-1-yl]-3-(1-naphthyl)-propionamide



C₃₆ H₃₄ N₄ O₃; Mol wt: 570.6896

ACTION – An inhibitor of LFA-1/ICAM-1, ICAM-2 or ICAM-3 interactions with potential for the treatment of ischemia-reperfusion disorders, transplant rejection, septic shock, acute or chronic inflammatory and autoimmune diseases, skin disorders, inflammatory bowel disease and ocular disorders. *In vitro*, compound inhibited the binding of human ICAM-1 to immobilized human LFA-1 (IC₅₀ = 0.07 μ M). *In vivo*, it was active in a murine model of allergic contact dermatitis, producing 40% inhibition of oxazolone-induced ear swelling when given to sensitized mice at a dose of 3 mg/kg p.o. 2 h and immediately before challenge, and 50% inhibition when applied topically at a concentration of 10 mM 30 min after challenge. A representative compound from a series of substituted diazepanes.

SOURCE – Novartis.

REFERENCES

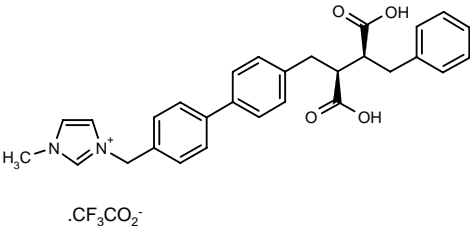
1. Albert, R. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Substd. diazepanes*. WO 0127102.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

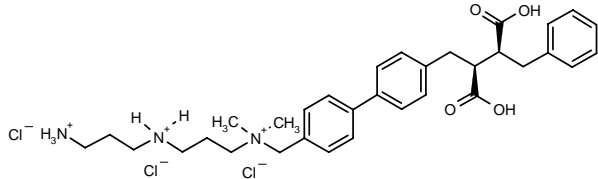
304553

3-[4'-[2(S),3(S)-Dicarboxy-4-phenylbutyl]biphenyl-4-ylmethyl]-1-methyl-1*H*-imidazol-3-ium trifluoroacetate

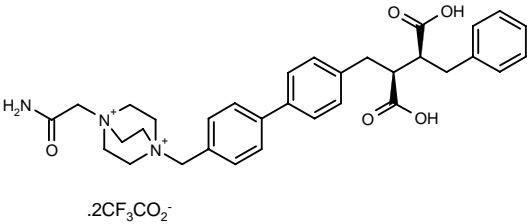


C31 H29 F3 N2 O6; Mol wt: 582.5721

ACTION – A representative compound from a series of substituted succinic acid derivatives with metallo-β-lactamase-inhibitory activity, potentially useful as a potentiator of β-lactam antibiotics for the treatment of bacterial infections. Other specifically claimed compounds include the following:



304554: C33 H46 Cl3 N3 O4



304555: C37 H39 F6 N3 O9

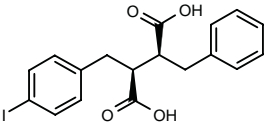
SOURCE – Merck & Co.

REFERENCES

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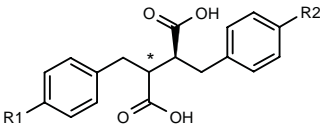
304557

2(S)-Benzyl-3(S)-(4-iodobenzyl)succinic acid



C18 H17 I O4; Mol wt: 424.2283

ACTION – A representative compound from a series of substituted succinic acid derivatives with metallo-β-lactamase-inhibitory activity, potentially useful as a potentiator of β-lactam antibiotics for the treatment of bacterial infections. Other specifically claimed compounds include the following:



Compound	R1	R2	* Isomer	Formula
304558	H	Ph	R	C ₂₄ H ₂₂ O ₄
304559	4-MeO-Ph	H	S	C ₂₅ H ₂₄ O ₅
304560	H	Ph	S	C ₂₄ H ₂₂ O ₄

SOURCE – Merck & Co.

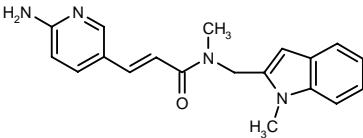
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ANTIBACTERIAL DRUGS

303776

3-(6-Aminopyridin-3-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-2(*E*)-propenamide



C19 H20 N4 O; Mol wt: 320.3940

ACTION – Antibacterial agent that acts by inhibiting Fab I (previously known as EnvM), an enzyme that is essential to bacterial fatty acid biosynthesis. Compound may be used in combination with known antibiotics and may also be of use as an antifungal agent.

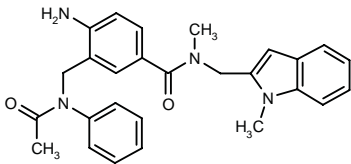
SOURCE – GlaxoSmithKline.

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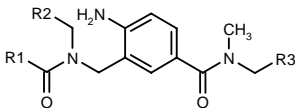
303780

3-(*N*-Acetyl-*N*-phenylaminomethyl)-4-amino-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)benzamide



C27 H28 N4 O2; Mol wt: 440.5442

ACTION – Antibacterial agent that acts by inhibiting Fab I (previously known as EnvM), an enzyme that is essential to bacterial fatty acid biosynthesis. Compound may be used in combination with known antibiotics and may also be of use as an antifungal agent. Other specifically claimed compounds from this series of indole derivatives are:



Compound	R1	R2	R3	Formula
303784	Me	CH2Ph	1-Me-2-indolyl	C ₂₉ H ₃₂ N ₄ O ₂
303793	i-BuCH(OH)	H	1-Me-2-indolyl	C ₂₆ H ₃₄ N ₄ O ₃
303794	OEt	H	1-Me-2-indolyl	C ₂₃ H ₂₈ N ₄ O ₃
303795	CH2OH	H	1-Me-2-indolyl	C ₂₂ H ₂₆ N ₄ O ₃
303796	Me	H	1-Me-3-indolyl	C ₂₂ H ₂₆ N ₄ O ₂
303797	Me	H	1-Me-2-indolyl	C ₂₂ H ₂₆ N ₄ O ₂
303798	3-indolyl-CH2CH(OH)	H	1-Me-2-indolyl	C ₃₁ H ₃₃ N ₅ O ₃
303799	4-OH-Ph	H	1-Me-2-indolyl	C ₂₇ H ₂₈ N ₄ O ₃
303800	CH2CH2SO2Ph	H	1-Me-2-indolyl	C ₂₉ H ₃₂ N ₄ O ₄ S
303801	cyclopentyl-CH2	H	1-Me-2-indolyl	C ₂₇ H ₃₄ N ₄ O ₂

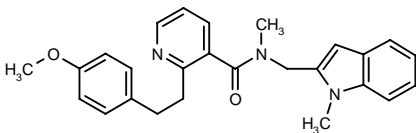
SOURCE – GlaxoSmithKline.

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1. Miller, W.H. et al. (SmithKline Beecham Corp.) *Fab I inhibitors*. WO 0126654.

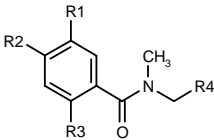
303803

2-[2-(4-Methoxyphenyl)ethyl]-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)pyridine-3-carboxamide



C26 H27 N3 O2; Mol wt: 413.5183

ACTION – Antibacterial agent that acts by inhibiting Fab I (previously known as EnvM), an enzyme that is essential to bacterial fatty acid biosynthesis. Compound may be used in combination with known antibiotics and may also be of use as an antifungal agent. Other specifically claimed compounds from this series of indole and indazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
303804	H	H	4-Pyr	1-Me-2-indolyl	C ₂₃ H ₂₁ N ₃ O
303805	H	H	3-furyl	1-Me-2-indolyl	C ₂₂ H ₂₀ N ₂ O ₂
303807	H	H	3-AcNH-Ph	1-Me-2-indolyl	C ₂₆ H ₂₆ N ₃ O ₂
303808	H	H	N(Me)2	1-Me-2-indolyl	C ₂₀ H ₂₃ N ₃ O
303810	H	NH2	OPh	1-Me-2-indolyl	C ₂₄ H ₂₃ N ₃ O ₂
303812	H	H	OPh	1-Me-3-indazolyl	C ₂₃ H ₂₁ N ₃ O ₂
303814	NH2	H	3-AcNH-Ph	1-Me-3-indolyl	C ₂₆ H ₂₆ N ₄ O ₂

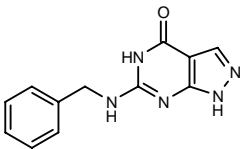
SOURCE – GlaxoSmithKline.

REFERENCES

1. Miller, W.H. et al. (SmithKline Beecham Corp.) *Fab I inhibitors*. WO 0126652.

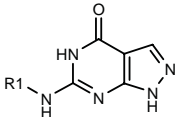
304139

6-Benzylamino-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



C12 H11 N5 O; Mol wt: 241.2529

ACTION – Antibacterial agent selective for Gram-positive microorganisms, a DNA polymerase III inhibitor that is especially useful against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), *Bacillus subtilis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae* and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds are:



Compound	R1	Formula
304140	3,4-(Me)2-PhCH2	C ₁₄ H ₁₅ N ₅ O
304141	3,4-(F)2-PhCH2	C ₁₂ H ₉ F ₂ N ₅ O
304142	3,4-(Cl)2-Ph	C ₁₁ H ₇ Cl ₂ N ₅ O

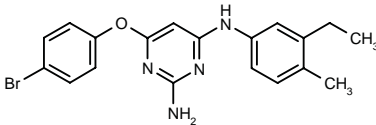
SOURCE – Merck & Co.

REFERENCES

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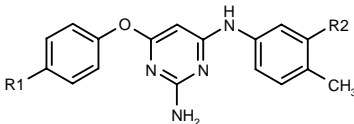
304143^{1,2}

6-(4-Bromophenoxy)-*N*⁴-(3-ethyl-4-methylphenyl)-pyrimidine-2,4-diamine



C19 H19 Br N4 O; Mol wt: 399.2901

ACTION – Antibacterial agent selective for Gram-positive microorganisms, a DNA polymerase III inhibitor that is especially useful against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), *Bacillus subtilis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae* and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds are:



Compound	R1	R2	Formula
304144 ^{1,2}	Cl	Et	C ₁₉ H ₁₉ ClN ₄ O
304145 ¹	Me	Et	C ₂₀ H ₂₂ N ₄ O
304146 ¹	Br	I	C ₁₇ H ₁₄ BrIN ₄ O

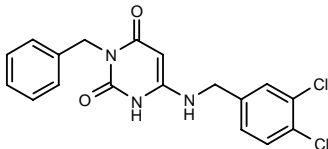
SOURCE – Merck & Co.

REFERENCES

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2. Ali, A. et al. *Design and synthesis of novel antibacterial agents with inhibitory activity against DNA polymerase III.* Bioorg Med Chem Lett 2001, 11(16): 2185.

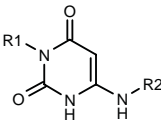
304147

3-Benzyl-6-(3,4-dichlorobenzylamino)uracil



C18 H15 Cl2 N3 O2; Mol wt: 376.2415

ACTION – Antibacterial agent selective for Gram-positive microorganisms, a DNA polymerase III inhibitor that is especially useful against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), *Bacillus subtilis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae* and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds are:



Compound	R1	R2	Formula
304148	CH2Ph	3-Et-4-Me-Ph	C ₂₀ H ₂₁ N ₃ O ₂
304149	Ph	3-Et-4-Me-Ph	C ₁₉ H ₁₉ N ₃ O ₂
304150	Ph	3,4-(Cl)2-PhCH2	C ₁₇ H ₁₃ Cl ₂ N ₃ O ₂
304151	allyl	3-I-4-Me-Ph	C ₁₄ H ₁₄ IN ₃ O ₂
304152	Et	3-I-4-Me-Ph	C ₁₃ H ₁₄ IN ₃ O ₂
304153	Et	3-Br-4-Me-Ph	C ₁₃ H ₁₄ BrN ₃ O ₂
304154	Me	3-I-4-Me-Ph	C ₁₂ H ₁₂ IN ₃ O ₂
304155	Pr	3-I-4-Me-Ph	C ₁₄ H ₁₆ IN ₃ O ₂
304156	Pr	3,4-(Cl)2-PhCH2	C ₁₄ H ₁₃ Cl ₂ N ₃ O ₂
304157	Et	3,4-(Cl)2-PhCH2	C ₁₃ H ₁₃ Cl ₂ N ₃ O ₂
304159	cyclohexyl	3-I-4-Me-Ph	C ₁₇ H ₂₀ IN ₃ O ₂
304160	Et	3,4-(Cl)2-Ph	C ₁₂ H ₁₁ Cl ₂ N ₃ O ₂

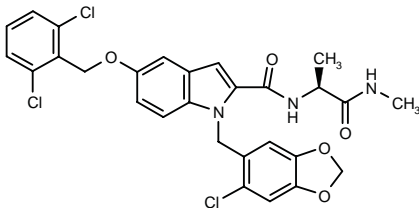
SOURCE – Merck & Co.

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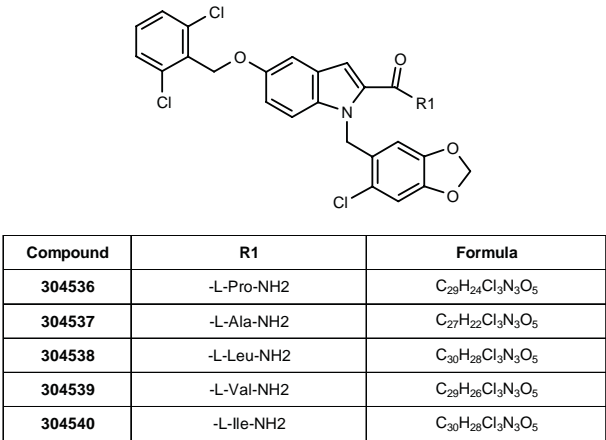
304535

N-[1-(6-Chloro-1,3-benzodioxol-5-ylmethyl)-5-(2,6-dichlorobenzyloxy)-1*H*-indol-2-ylcarbonyl]-*L*-alanine methylamide



C28 H24 Cl3 N3 O5; Mol wt: 588.8726

ACTION – Antibacterial agent reported to be active against a wide range of microorganisms including Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli* and *Klebsiella pneumoniae* and including antibiotic-resistant strains. It acts by inhibiting the fatty acid synthase FabH. Other specifically claimed compounds from this series of indole derivatives are:



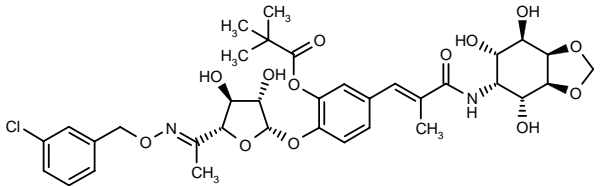
SOURCE – GlaxoSmithKline.

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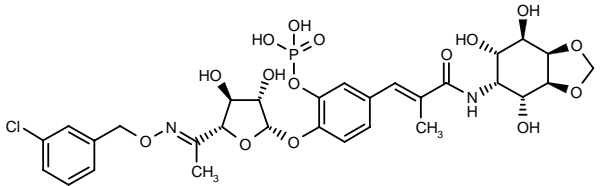
304579

2,2-Dimethylpropionic acid 2-[5(R)-[(1E)-N-(3-chloro-benzyloxy)ethanimidoyl]-3(S),4(S)-dihydroxytetrahydro-furan-2(S)-yloxy]-5-[2-[N-[(3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxyperhydro-1,3-benzodioxol-5-yl]carbamoyl]-1(E)-propenyl]phenyl ester



C35 H43 Cl N2 O13; Mol wt: 735.1787

ACTION – Antibacterial and antiprotozoal agent, a representative compound from a series of hygromycin A prodrugs reported to possess advantages over the parent drugs in terms of efficacy, formulation, solubility, side effects or stability. Compound is reported to be active in a mouse peritonitis model caused by i.p. injection of *Staphylococcus aureus*, with a PD₅₀ value in the range 12.5-100 mg/kg s.c. Another exemplified compound is:



304580: C30 H36 Cl N2 O15 P

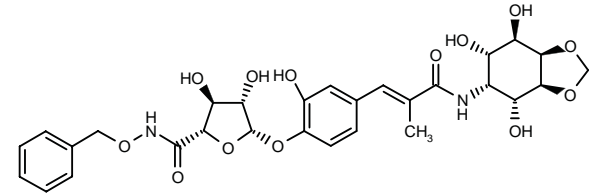
SOURCE – Pfizer.

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1. Kaneko, T. (Pfizer Products Inc.) *Hygromycin A prodrugs.* WO 0130793.

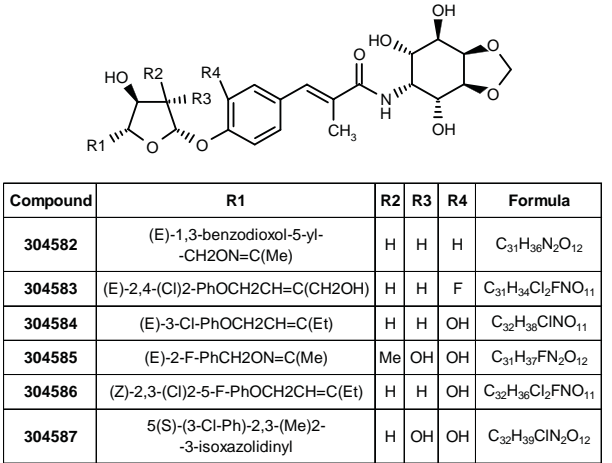
304581

3 (S),4 (S)-Dihydroxy-5 (S)-[2-hydroxy-4-[2-[N-[(3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxyperhydro-1,3-benzodioxol-5-yl]carbamoyl]-1-propenyl]phenoxy]-tetrahydrofuran-2(S)-carbohydroxamic acid benzyl ester



C29 H34 N2 O13; Mol wt: 618.5886

ACTION – Antibacterial and antiprotozoal hygromycin A derivative with activity against both Gram-negative and Gram-positive bacteria and protozoa. Other specifically claimed compounds include the following:



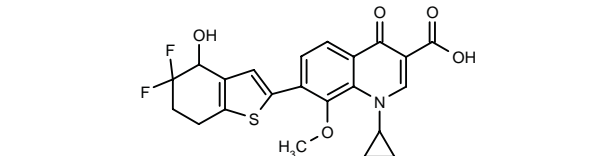
SOURCE – Pfizer.

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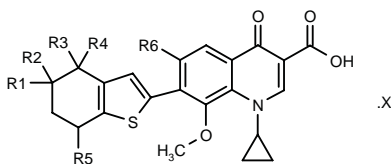
304705

1-Cyclopropyl-7-(5,5-difluoro-4-hydroxy-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C22 H19 F2 N O5 S; Mol wt: 447.4561

ACTION – Antibacterial quinolone with MIC values of 0.03, 0.125 and 0.125 µg/ml, respectively, against *Enterococcus faecalis* PIU 1967, *Escherichia coli* JUHL and *Streptococcus pneumoniae* ATCC 6303, and MICs of 0.004 µg/ml or less against *Staphylococcus aureus* ATCC 6538P and *Haemophilus influenzae* DILL AMP R. Other exemplified compounds from this series of quinoline and naphthyridine carboxylic acid derivatives are:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
304706	H	H	CH2OH	H	H	H		C ₂₃ H ₂₃ NO ₅ S
304707	H	H	H	H	NH2	F	HCl	C ₂₂ H ₂₁ FN ₂ O ₄ S.HCl
304708	Br	H	-O-		H	H		C ₂₂ H ₁₈ BrNO ₅ S
304709	(E,Z)-HON=		H	H	H	H		C ₂₂ H ₂₀ N ₂ O ₅ S

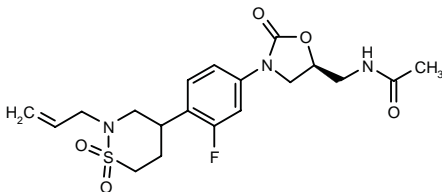
SOURCE – Abbott.

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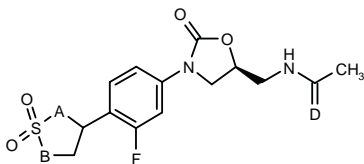
304809

N-[3-[4-(2-Allyl)-1,1-dioxoperhydro-1,2-thiazin-4-yl)-3-fluorophenyl]-2-oxoxazolidin-5(S)-ylmethyl]acetamide



C19 H24 F N3 O5 S; Mol wt: 425.4786

ACTION – Oxazolidinone antibacterial agent active against Gram-positive bacteria such as multidrug-resistant staphylococci and streptococci, Gram-negative bacteria such as *Haemophilus influenzae* and *Moraxella catarrhalis*, as well as anaerobic organisms such as *Bacteroides* and *Clostridium* species and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. Other specifically claimed compounds from this series of sultam- and sultone-derived oxazolidinones are:



Compound	A	B	D	Formula
304810	-(CH2)2-	-NH-	-O-	C ₁₆ H ₂₀ FN ₃ O ₅ S
304811	-(CH2)2-	-NH-	-S-	C ₁₆ H ₂₀ FN ₃ O ₄ S ₂
304812	-(CH2)2-	-N(Me)-	-S-	C ₁₇ H ₂₂ FN ₃ O ₄ S ₂
304813	-(CH2)2-	-O-	-S-	C ₁₆ H ₁₉ FN ₂ O ₅ S ₂
304814	-CH2-	-NH-	-S-	C ₁₅ H ₁₈ FN ₃ O ₄ S ₂
304815	-(CH2)2-	-N(Me)-	-O-	C ₁₇ H ₂₂ FN ₃ O ₅ S

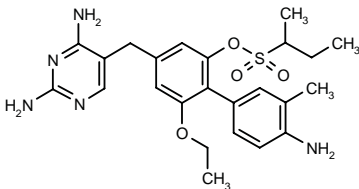
SOURCE – Pharmacia.

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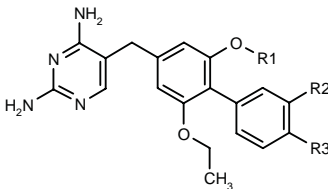
304828

Butane-2-sulfonic acid 4'-amino-4-(2,4-diaminopyrimidin-5-ylmethyl)-6-ethoxy-3'-methylbiphenyl-2-yl ester



C24 H31 N5 O4 S; Mol wt: 485.6059

ACTION – Antibacterial agent active against various microorganisms including multidrug-resistant Gram-positive strains such as *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Staphylococcus aureus* and opportunistic pathogens such as *Pneumocystis carinii* that acts by inhibiting bacterial dihydrofolate reductase (DHFR). Compound was very potent against purified DHFR from trimethoprim- and penicillin-resistant *S. pneumoniae* SP1/1 and from trimethoprim-resistant *S. aureus* 157/4696 (IC₅₀ = 0.0046 and 0.062 μM, respectively, vs. 3.1 and 19 μM, respectively, for trimethoprim and 0.19 and 2 μM, respectively, for epiroprim). In addition, it exhibited MIC values of 0.5 and 1 μg/ml, respectively, against *S. pneumoniae* SP 1/1 and methicillin-resistant *S. aureus* 101, compared to respective MIC values of > 32 and 32 μg/ml for trimethoprim and 4 and 16 μg/ml for epiroprim. Other compounds from this series of substituted 5-benzyl-2,4-diaminopyrimidines include the following:



Compound	R1	R2	R3	Formula
304829	cyclobutyl-SO2	Me	NH2	C ₂₄ H ₂₉ N ₅ O ₄ S
304830	4-morpholinyl-SO2	H	NHMe	C ₂₄ H ₃₀ N ₆ O ₅ S
304831	SO2N(Me)2	NH2	Me	C ₂₂ H ₂₈ N ₆ O ₄ S
304833	SO2CH(Me)Et	H	NH2	C ₂₃ H ₂₉ N ₅ O ₄ S
304834	i-PrSO2	H	NH2	C ₂₂ H ₂₇ N ₅ O ₄ S
304835	SO2CH(Me)Et	NH2	H	C ₂₃ H ₂₉ N ₅ O ₄ S
304836	cyclopropyl-N(Me)SO2	H	NH2	C ₂₃ H ₂₈ N ₆ O ₄ S
304837	i-PrSO2	NH2	H	C ₂₂ H ₂₇ N ₅ O ₄ S
304838	i-PrSO2	Me	NH2	C ₂₃ H ₂₉ N ₅ O ₄ S
304839	cyclopropyl-CH2	NH2	H	C ₂₃ H ₂₇ N ₅ O ₂
304840	Et	NH2	H	C ₂₁ H ₂₅ N ₅ O ₂

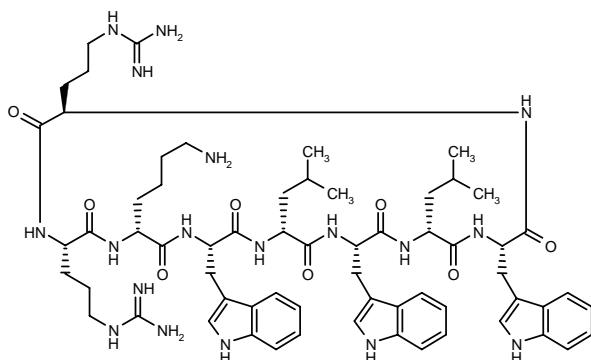
SOURCE – Roche.

REFERENCES

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306572

Cyclo(D-arginyl-L-arginyl-D-lysyl-L-tryptophyl-D-leucyl-L-tryptophyl-D-leucyl-L-tryptophyl)



C63 H88 N18 O8; Mol wt: 1225.5060

ACTION – Antibacterial agent, a cyclic D,L- α -peptide active *in vitro* against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* (MIC = 6 and 15 μ g/ml, respectively). In the presence of large amounts of plasma proteins, the antibacterial activity of the peptide remained unchanged and its hemolytic activity was reduced (HD₅₀ = 50 μ g/ml). Moreover, compound was stable in the presence of trypsin, α -chymotrypsin, subtilisin and murine blood plasma, with no significant degradation. Results from preliminary toxicology studies in mice showed no signs of toxicity at up to 17.5 mg/kg s.c. or i.p. *In vivo*, compound at a dose of 13 mg/kg protected mice from systemic infections caused by MRSA: 67 and 50% of mice that received the peptide i.p. and s.c., respectively, survived during the course of a 7-day study.

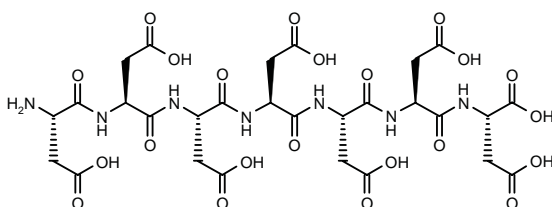
SOURCE – Scripps Research Institute, La Jolla, CA (US).

REFERENCES

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307050

L-Aspartyl-L-aspartyl-L-aspartyl-L-aspartyl-L-aspartyl-L-aspartyl-L-aspartic acid



C28 H37 N7 O22; Mol wt: 823.6273

ACTION – Antimicrobial anionic peptide isolated from ovine surfactants, active *in vitro* against *Pasteurella haemolytica* (MIC = 80 mM) and *in vivo* in a lamb model of acute pneumonia. When given to *P. haemolytica*-infected lambs as a single intratracheal dose of 0.5 mg, it reduced pulmonary inflammation and the concentration of *P. haemolytica* in lung tissues. Potentially useful for the treatment of pulmonary infections.

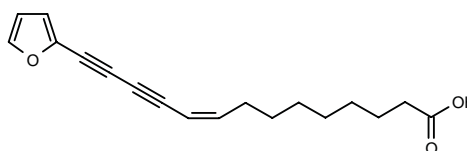
SOURCES – Iowa State University, Ames, IA (US); US Department of Agriculture (US).

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2. Brogden, K.A. et al. *Detection of anionic antimicrobial peptides in ovine bronchoalveolar fluid and respiratory epithelium*. Infect Immun 1998, 66(12): 5948.
3. Brogden, K.A. et al. *Isolation of an ovine pulmonary surfactant-associated anionic peptide bactericidal for Pasteurella haemolytica*. Proc Natl Acad Sci USA 1996, 93(1): 412.
4. Brogden, K.A. et al. *Small, anionic, and charge-neutralizing propeptide fragments of zymogens are antimicrobial*. Antimicrob Agents Chemother 1997, 41(7): 1615.
5. Kalfa, V.C. et al. *Suppression of Mannheimia (Pasteurella) haemolytica serovar 1 infection in lambs by intrapulmonary administration of ovine antimicrobial anionic peptide*. Int J Antimicrob Agents 2001, 17(6): 505.

ANTIFUNGAL AGENTS**303651**

14-(2-Furyl)-9(Z)-tetradecene-11,13-diynoic acid



C18 H20 O3; Mol wt: 284.3530

ACTION – Antifungal and antibacterial agent, a representative compound from a series of enediyne derivatives that can be isolated from plant cell cultures of *Anarrhinum bellidifolium* or *Anarrhinum corsicum* (Scrophulariaceae) or obtained by chemical synthesis. *In vitro*, compound was active against *Candida albicans* including fluconazole-resistant strains, with MIC values in the range 0.625-5 ng/ml. In addition, compound was tested against strains of *Candida keyfer* (MIC = 10 ng/ml), *Candida tropicalis* (MIC = 5 ng/ml), *Candida krusei* (MIC = 50 ng/ml), *Candida glabrata* (MIC = 5-12.5 ng/ml), *Saccharomyces cerevisiae* (MIC = 0.25-1 μ g/ml), *Aspergillus fumigatus* (MIC = 200 μ g/ml), *Staphylococcus aureus* (MIC = 50 μ g/ml), *Enterococcus faecalis* (MIC = 12.5 μ g/ml), *Escherichia coli* (MIC > 200 μ g/ml), *Trichophyton rubrum* (MIC = 0.001 μ g/ml), *Trichophyton mentagrophytes* (MIC = 0.001 mg/ml), *Trichophyton tonsurans* (MIC = 0.001 μ g/ml) and *Microsporium canis* (MIC = 0.001 μ g/ml).

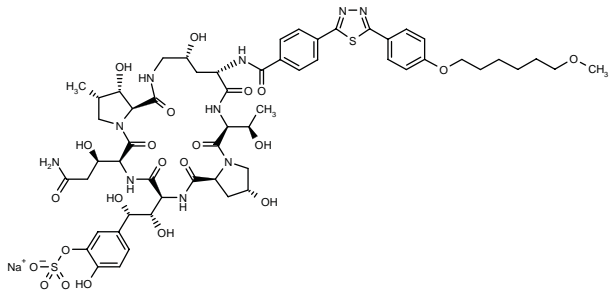
SOURCE – Phytera.

REFERENCES

1. Cui, B. et al. (Phytera, Inc.) *Antifungal enediynes*. WO 0125197.

304415

(2*R*,6*S*,9*S*,11*R*,14*aS*,15*S*,16*S*,20*S*,23*S*,25*aS*)-20-[3-Amino-1(*R*)-hydroxy-3-oxopropyl]-23-[1(*S*),2(*S*)-dihydroxy-2-[4-hydroxy-3-(sulfooxy)phenyl]ethyl]-2,11,15-trihydroxy-6-[1(*R*)-hydroxyethyl]-9-[4-[5-[4-(6-methoxyhexyloxy)phenyl]-1,3,4-thiadiazol-2-yl]-benzamido]-16-methylperhydrodipyrrolo[2,1-*c*:2',1'-]-[1,4,7,10,13,16]hexaazacycloheneicosine-5,8,14,19,22,25-hexaone sodium salt



C57 H73 N10 Na O22 S2; Mol wt: 1337.3740

ACTION – Antifungal agent with β -1,3-glucan synthase-inhibitory activity, reported to be active against *Aspergillus*, *Cryptococcus*, *Candida*, *Mucor*, *Actinomyces*, *Histoplasma*, dermatophytes, *Malassezia* and *Fusarium* spp., as well as against *Pneumocystis carinii*. *In vitro*, compound exhibited an MIC value of 0.0625 μ g/ml against *Candida albicans* FP-633. A representative compound from a series of cyclic hexapeptides.

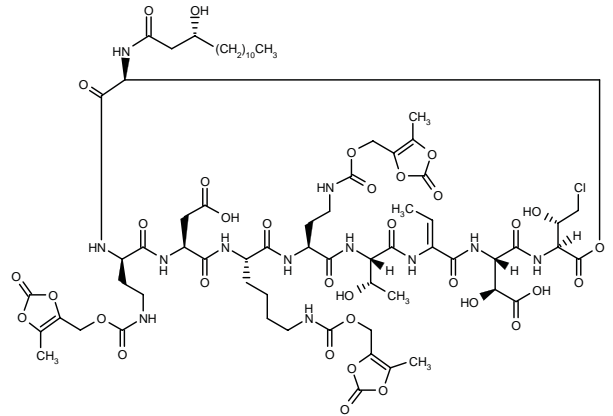
SOURCE – Fujisawa.

REFERENCES

1. Ohki, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Cyclic hexapeptides with antimicrobial activity*. US 6232290, WO 9940108.

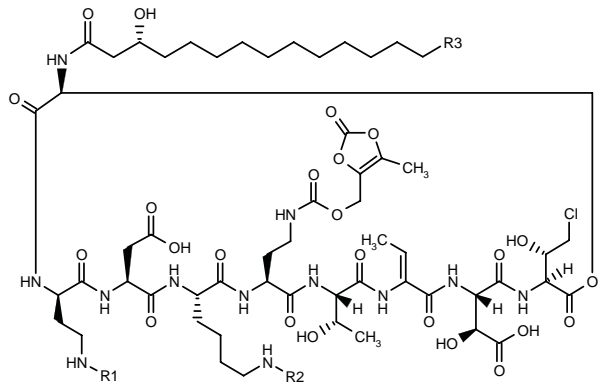
305901

N-[3(*R*)-Hydroxytetradecanoyl]-L-seryl-4-(5-methyl-2-oxo-1,3-dioxol-4-ylmethoxycarboxamido)-D-2-aminobutyryl-L-aspartyl-*N*⁶-(5-methyl-2-oxo-1,3-dioxol-4-ylmethoxycarboxamido)-L-lysyl-4-(5-methyl-2-oxo-1,3-dioxol-4-ylmethoxycarboxamido)-L-2-aminobutyryl-L-allothreonyl-(*Z*)-2,3-didehydro-2-aminobutyryl-3(*S*)-hydroxy-L-aspartyl-4-chloro-L-threonine C-1.9-*O*-3.1-lactone



C69 H99 Cl N12 O34; Mol wt: 1676.0440

ACTION – Oxodioxolenylmethyl carbamate prodrug of pseudomycin B with comparable *in vivo* antifungal activity to the parent compound against disseminated candidiasis in mice and an improved safety margin This prodrug did not induce tail vein irritation and showed no histamine-related pathology in rodents, in contrast to pseudomycin B. Other prodrugs are:



Compound	R1=R2	R3	Formula
305895	H	H	C ₅₇ H ₉₁ ClN ₁₂ O ₂₄
305905	5-Me-2-oxo-1,3-dioxol-4-yl-CH ₂ OCO	Et	C ₇₁ H ₁₀₃ ClN ₁₂ O ₃₄

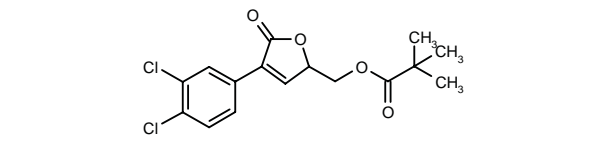
SOURCE – Lilly.

REFERENCES

1. Chen, S.H. et al. (Eli Lilly and Company) *Pseudomycin prodrugs*. WO 0105813.
2. Sun, X. et al. *Synthesis and evaluation of oxodioxolenylmethyl carbamate prodrugs of pseudomycins*. J Med Chem 2001, 44(16): 2671.

306602

2,2-Dimethylpropionic acid 4-(3,4-dichlorophenyl)-5-oxo-2,5-dihydrofuran-2-ylmethyl ester



C16 H16 Cl2 O4; Mol wt: 343.2044

ACTION – Antifungal agent with high *in vitro* activity against *Candida albicans*, *Candida krusei*, *Candida glabrata* and *Candida tropicalis* (MIC = 0.17, 2.67, 0.17 and 1.34 μ g/ml, respectively, after 24-h exposure), as well as against *Aspergillus fumigatus* (MIC = 0.67 μ g/ml after 24-h exposure); its activity against *A. fumigatus* was comparable to amphotericin B and superior to ketoconazole. Preliminary toxicity experiments in mice showed moderate toxicity (LD₅₀ = 54 mg/kg i.p.) and good absorption through the peritoneum.

SOURCE – Univerzita Karlova, Praha (CZ).

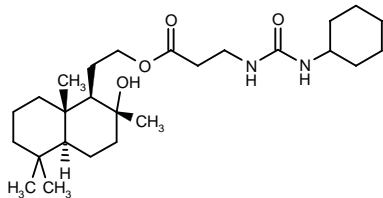
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1. Pour, M. et al. *3-Phenyl-5-acyloxymethyl-2H,5H-furan-2-ones: Synthesis and biological activity of a novel group of potential antifungal drugs*. J Med Chem 2001, 44(17): 2701.

ALB-072

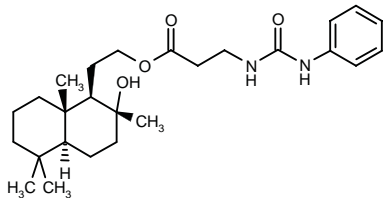
304907

3-(3-Cyclohexylureido)propionic acid 2-[(1*R*,2*R*,4*aS*,8*aS*)-2-hydroxy-2,5,5,8*a*-tetramethylperhydronaphthalen-1-yl]-ethyl ester



C26 H46 N2 O4; Mol wt: 450.6594

ACTION – Antifungal agent, particularly active against an azole-resistant strain of *Aspergillus fumigatus* (IC₈₀ = 4 µg/ml). When tested against *A. fumigatus* infection in mice, the survival rate was 40% at 2 and 10 mg/kg p.o. Another exemplified hydronaphthalene derivative is:



ALB-077 [304908]: C26 H40 N2 O4

SOURCE – Toagosei.

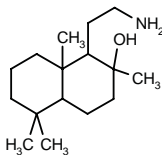
REFERENCES

1. Takahashi, A. et al. (Toagosei Co., Ltd.) *Amino acid or peptide-added hydronaphthalene derivs.* JP 2001106662.

ALB-245

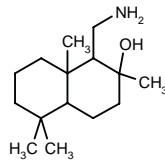
304909

1-(2-Aminoethyl)-2,5,5,8*a*-tetramethylperhydronaphthalen-2-ol



C16 H31 N O; Mol wt: 253.4269

ACTION – Antifungal agent, particularly active against an azole-resistant strain of *Aspergillus fumigatus* (IC₈₀ = 8 µg/ml), a sensitive strain of *A. fumigatus* (IC₈₀ = 4 µg/ml) and *Candida albicans* (IC₈₀ = 16 µg/ml). When tested against *A. fumigatus* infection in mice, the survival rate was at least 60% at 10 mg/kg p.o. Another exemplified hydronaphthalene derivative is:



ALB-031 [304910]: C15 H29 N O

SOURCE – Toagosei.

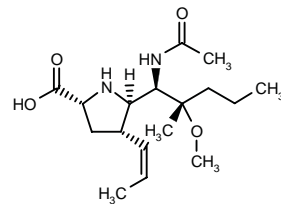
REFERENCES

1. Takahashi, A. et al. (Toagosei Co., Ltd.) *Hydronaphthyl alkyl amine.* JP 2001106660.

ANTIVIRAL DRUGS

304097

(-)-5-(*R*)-[1(*R*)-Acetamido-2(*S*)-methoxy-2-methylpentyl]-4(*S*)-[1(*Z*)-propenyl]pyrrolidine-2(*R*)-carboxylic acid



C17 H30 N2 O4; Mol wt: 326.4340

ACTION – Neuraminidase inhibitor reported to inhibit influenza A and B neuraminidase, potentially useful for the treatment or prevention of influenza infections. A representative compound from a series of pyrrolidine derivatives.

SOURCE – Abbott.

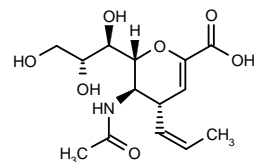
REFERENCES

1. Maring, C.J. et al. (Abbott Laboratories Inc.) *Inhibitors of neuraminidases.* WO 0128996.

304098

5-Acetamido-2,6-anhydro-3,4,5-trideoxy-4-[1(*Z*)-propenyl]-D-*glycero*-D-*galacto*-non-2-enonic acid

5(*R*)-Acetamido-4(*S*)-[1(*Z*)-propenyl]-6(*R*)-[1(*S*),2(*R*),3-trihydroxypropyl]-5,6-dihydro-4*H*-pyran-2-carboxylic acid



C14 H21 N O7; Mol wt: 315.3199

ACTION – Neuraminidase inhibitor reported to inhibit influenza A and B neuraminidase, potentially useful for the treatment or prevention of influenza infections. A representative compound from a series of dihydropyran derivatives.

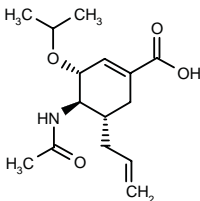
SOURCE – Abbott.

REFERENCES

1. Maring, C.J. et al. (Abbott Laboratories Inc.) *Neuraminidase inhibitors*. WO 0129021.

304099

4(R)-Acetamido-5(S)-allyl-3(R)-isopropoxy-1-cyclohexene-1-carboxylic acid



C15 H23 N O4; Mol wt: 281.3497

ACTION – Neuraminidase inhibitor reported to inhibit influenza A and B neuraminidase, potentially useful for the treatment or prevention of influenza infections. A representative compound from a series of 1-cyclohexene-1-carboxylic acids and 1-cyclohexene-1-carboxylates.

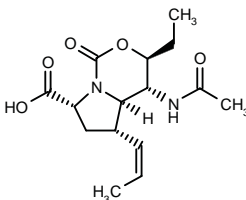
SOURCE – Abbott.

REFERENCES

1. Maring, C.J. et al. (Abbott Laboratories Inc.) *1-Cyclohexene-1-carboxylic acid and 1-cyclohexene-1-carboxylates as neuraminidase inhibitors*. WO 0128981.

304100

(3S,4R,4aR,5S,7R)-4-Acetamido-3-ethyl-1-oxo-5-[1(Z)-propenyl]perhydropyrrolo[1,2-c][1,3]oxazine-7-carboxylic acid



C15 H22 N2 O5; Mol wt: 310.3478

ACTION – Neuraminidase inhibitor reported to inhibit influenza A and B neuraminidase, potentially useful for the treatment or prevention of influenza infections. A representative compound from a series of bicyclic compounds.

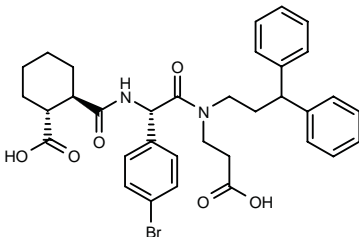
SOURCE – Abbott.

REFERENCES

1. Maring, C.J. et al. (Abbott Laboratories Inc.) *Neuraminidase inhibitors*. WO 0129050.

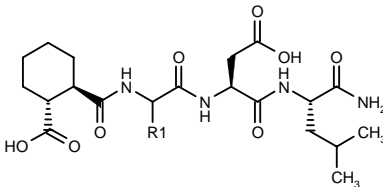
304817

(1R,2R)-2-[N-[1(S)-(4-Bromophenyl)-1-[N-(2-carboxyethyl)-N-(3,3-diphenylpropyl)carbamoyl]-methyl]carbamoyl]cyclohexanecarboxylic acid

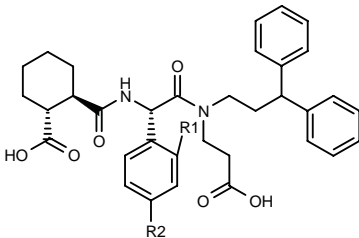


C34 H37 Br N2 O6; Mol wt: 649.5783

ACTION – Agent for the treatment of hepatitis C virus (HCV) infection or related conditions that acts by inhibiting HCV NS3 protease (IC₅₀ = 1.7 μM). Other exemplified compounds from this series of carbocyclic derivatives include the following:



Compound	R1	Formula
304818	(S)-cyclohexyl-CH2	C ₂₇ H ₄₄ N ₄ O ₈
304819	3-[(Ph)2CHCH2COO]-Ph	C ₄₁ H ₄₈ N ₄ O ₁₀



Compound	R1	R2	Formula
304820	H	CF3	C ₃₆ H ₃₇ F ₃ N ₂ O ₆
304821	F	H	C ₃₄ H ₃₇ FN ₂ O ₆

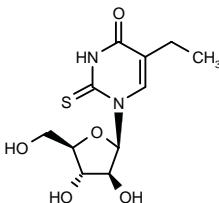
SOURCE – Istituto di Ricerche di Biologia Molecolare P. Angeletti.

REFERENCES

1. Nicholls, K.M. et al. (Istituto di Ricerche di Biologia Molecolare P. Angeletti SpA) *HCV NS3 protease inhibitors*. WO 0132691.

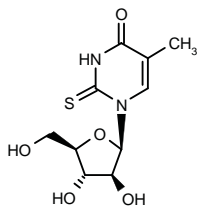
304911

1-(β-D-Arabinofuranosyl)-5-ethyl-2-thiouracil



C11 H16 N2 O5 S; Mol wt: 288.3224

ACTION – Antiviral agent, active against herpes simplex virus type 1 (HSV-1; $EC_{50} = 0.032 \mu\text{g/ml}$). This compound exhibited a CC_{50} value $> 100 \mu\text{g/ml}$ (selectivity index $> 3,100$) using RPMI 8226 cells. Another exemplified 5-alkyl-2-thiouracil arabinoside is:



304913: C10 H14 N2 O5 S

SOURCE – Toagosei.

REFERENCES

1. Saneyoshi, M. et al. (Toagosei Co., Ltd.) 5-Alkyl-2-thiouracil arabinoside and antiviral agents containing the same. JP 2001097995.

CDR-H1C13

304918

L-Cysteinyl-L-seryl-L-phenylalanyl-L-threonyl-L-aspartyl-L-tyrosyl-L-valyl-L-leucyl-L-isoleucyl-L-tryptophyl-L-valyl-L-lysyl-L-cysteine cyclic (1-13)-disulfide

C74 H107 N15 O19 S2; Mol wt: 1574.8770

ACTION – Antiviral agent that inhibits hepatitis C virus (HCV) NS3 serine protease, as demonstrated *in vitro*. Another exemplified cyclic peptide is:

L-Cysteinyl-L-threonyl-L-aspartyl-L-tyrosyl-L-valyl-L-leucyl-L-isoleucyl-L-tryptophyl-L-cysteine cyclic (1-9)-disulfide

CDR-H1C9 [304920]: C51 H72 N10 O14 S2

SOURCE – Japan Energy.

REFERENCES

1. Misawa, S. (Japan Energy Corp.) Cyclic peptide and serine protease inhibitors. JP 2001103993.

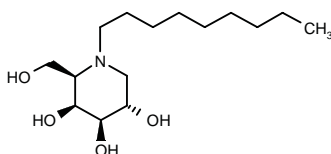
N-NONYL-DGJ

306649

(2R,3S,4R,5S)-2-(Hydroxymethyl)-1-nonyl-3,4,5-piperidinetriol

1,5-Dideoxy-1,5-(nonylimino)-D-galactitol

N-Nonyl-deoxygalactojirimycin
AlkovirTM



C15 H31 N O4; Mol wt: 289.4129

ACTION – Antiviral agent active against hepatitis B virus (HBV), an orally available alkyl derivative of galactose that exerts potent antiviral activity against HBV in the absence of glucosidase inhibition. In contrast to glucosidase inhibitors, this compound markedly decreased intracellular levels of HBV DNA without inhibiting DNA polymerase. It may act by a different mechanism, probably preventing the proper encapsidation of the HBV pregenomic RNA.

SOURCES – University of Oxford, Oxford (GB); Thomas Jefferson University, Philadelphia, PA (US).

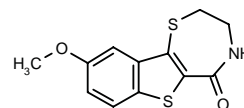
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2. Mehta, A. et al. Inhibition of hepatitis B virus DNA replication by imino sugars without the inhibition of the DNA polymerase: Therapeutic implications. Hepatology 2001, 33(6): 1488.
3. Mellor, H.R. et al. High performance cation-exchange chromatography and pulsed amperometric detection for the separation, detection, and quantitation of N-alkylated imino sugars in biological samples. Anal Biochem 2000, 284(1): 136.

PD-146626*

228816

9-Methoxy-2,3,4,5-tetrahydro[1]benzothieno[2,3-f]-1,4-thiazepin-5-one



C12 H11 N O2 S2; Mol wt: 265.3550

ACTION – Antiviral agent active against herpes simplex virus type 1 (HSV-1; $EC_{50} = 0.1 \mu\text{M}$), proven to inhibit viral immediate early gene expression probably via a host cell pathway. Compound did not show antiinflammatory effects or detectable antiviral activity against either HIV or influenza virus. However, it inhibited human cytomegalovirus (HCMV) replication to a similar extent as HSV-1. Although the pharmacokinetic properties of compound preclude its future development as a clinical candidate, it represents a lead for the further development of small-molecule inhibitors of HSV-1 immediate early gene expression.

SOURCE – Pfizer.

REFERENCES

1. Boschelli, D.H. et al. (Pfizer Inc.) Benzothioephene, benzofuran and indolethiazepinones, oxazepinones and diazepinones as inhibitors of cell adhesion and as inhibitors of HIV. EP 0749434, JP 1997509961, US 5489586, WO 9524408.
2. Gracheck, S.J. (Pfizer Inc.) Use of thiazepine, oxazepine and diazepine cpds. for inhibiting HIV, herpesvirus and suppressing the immune system. EP 0817635, JP 1999502814, WO 9629077.
3. Boulware, S.L. et al. Identification and characterization of a benzothioephene inhibitor of herpes simplex virus type 1 replication which acts at the immediate early stage of infection. Antivir Res 2001, 51(2): 111.
4. Khatana, S.S. et al. Preparation of benzothieno[2,3-f]-1,4-oxazepin- and -thiazepin-5(2H)-ones and of benzothieno[3,2-e]-1,4-diazepin-5-ones. J Org Chem 1996, 61(17): 6060.

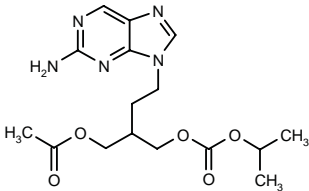
*Identified compound **228816** Drug Data Rep 1996, 018(02): 0174.

SK-1899*

279899

Acetic acid 4-(2-amino-9*H*-purin-9-yl)-2-(isopropoxycarbonyloxymethyl)butyl ester

9-[4-(Acetoxy)-3-(isopropoxycarbonyloxymethyl)butyl]-2-aminopurine



C16 H23 N5 O5; Mol wt: 365.3877

ACTION – Antiviral agent, an orally available penciclovir prodrug with antiviral efficacy superior to that of the two penciclovir prodrugs famciclovir and valaciclovir against herpes simplex virus type 1 (HSV-1) and duck hepatitis B virus. Pharmacokinetic studies in rats and dogs showed that compound was well absorbed following oral administration and rapidly metabolized to penciclovir; high urinary recovery of penciclovir were seen in rats and dogs (36.1 and 36.3% of dose, respectively). Moreover, safety and general pharmacology experiments demonstrated no adverse effects at antiviral doses.

SOURCE – SK Chemicals.

REFERENCES

1. Choi, W.S. et al. *Pharmacokinetic studies of 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyl-oxybut-1-yl)purine, an oral prodrug for the antiviral agent penciclovir.* Drug Metab Dispos 2001, 29(7): 945.

2. Kim, D.-K. et al. *Synthesis and evaluation of 2-amino-9-(3-acyloxymethyl-4-alkoxycarbonyloxybut-1-yl)purines and 2-amino-9-(3-alkoxycarbonyloxymethyl-4-alkoxycarbonyloxybut-1-yl)purines as potential prodrugs of penciclovir.* Bioorg Med Chem 1999, 7(8): 1715.

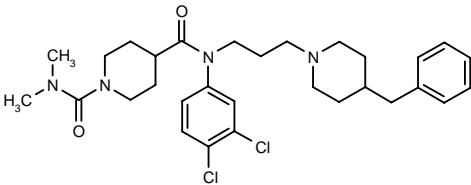
3. Ryu, K.H. et al. *General pharmacology of the new antiviral agent SK 1899.* Arzneim-Forsch Drug Res 2000, 50(4): 395.

*Identified compound **279899** Drug Data Rep 1999, 021(11): 0998.

AIDS MEDICINES

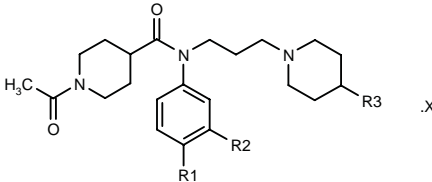
303667

*N*⁴-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*⁴-(3,4-dichlorophenyl)-*N*¹,*N*¹-dimethylpiperidine-1,4-dicarboxamide



C30 H40 Cl2 N4 O2; Mol wt: 559.5780

ACTION – Antiviral agent for AIDS, a selective chemokine CCR5 receptor antagonist (99% inhibition of [¹²⁵I]-RANTES binding in human CCR5-expressing CHO cells at 1 μM). Other exemplified compounds from this series of cyclic amine derivatives include the following:



Compound	R1	R2	R3	X	Formula
303670	H	H	CH2Ph		C ₂₉ H ₃₉ N ₃ O ₂
303671	Cl	Cl	4-F-PhCH2	HCl	C ₂₉ H ₃₆ Cl ₂ FN ₃ O ₂ ·HCl
303672	H	Cl	2-benzothiazolyl-S	HCl	C ₂₉ H ₃₅ ClN ₄ O ₂ S ₂ ·HCl

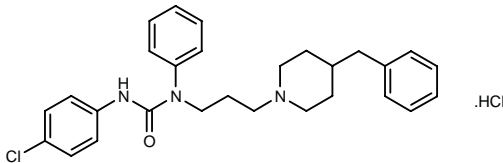
SOURCE – Takeda.

REFERENCES

1. Imamura, S. et al. (Takeda Chemical Industries, Ltd.) *Cyclic amine cpds. as CCR5 antagonists.* WO 0125200.

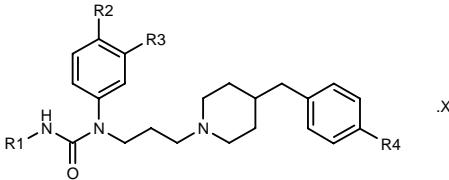
304008

N-[3-(4-Benzylpiperidin-1-yl)propyl]-*N*'-(4-chlorophenyl)-*N*-phenylurea hydrochloride



C28 H32 Cl N3 O . HCl; Mol wt: 498.4947

ACTION – Chemokine CCR5 receptor antagonist, potentially useful for the treatment of HIV infection. This compound produced 98% inhibition of HIV-1 infection in MAGI-CCR5 cells at 0.32 μM. Other exemplified urea compounds include the following:



Compound	R1	R2	R3	R4	X	Formula
304009	Ph	H	H	H	HCl	C ₂₈ H ₃₃ N ₃ O·HCl
304010	Pr	H	H	H		C ₂₅ H ₃₅ N ₃ O
304011	4-Cl-Ph	Me	H	H	HCl	C ₂₉ H ₃₄ ClN ₃ O·HCl
304012	4-Cl-Ph	Cl	Cl	F		C ₂₈ H ₂₉ Cl ₃ FN ₃ O
304013	1-Naph	H	H	H		C ₃₂ H ₃₅ N ₃ O
304014	4-Cl-Ph	H	H	4-morpholinyl-SO2	HCl	C ₃₂ H ₃₉ ClN ₄ O ₄ S·HCl
304016	4-Cl-Ph	H	H	SO2Me	HCl	C ₂₉ H ₃₄ ClN ₃ O ₃ S·HCl

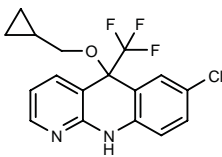
SOURCE – Takeda.

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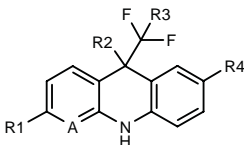
304103

7-Chloro-5-(cyclopropylmethoxy)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,8-naphthyridine



C17 H14 Cl F3 N2 O; Mol wt: 354.7576

ACTION – Antiviral agent, an inhibitor of HIV reverse transcriptase that is potentially useful for the treatment of HIV infection, alone or in combination with other HIV reverse transcriptase or HIV protease inhibitors. Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
304104	Me	cyclopropyl-CH2O	F	Cl	N	C ₁₈ H ₁₆ ClF ₃ N ₂ O
304105	H	NHPh	F	Cl	N	C ₁₉ H ₁₃ ClF ₃ N ₃
304106	H	cyclopropyl-CH2O	F	F	N(O)	C ₁₇ H ₁₄ F ₄ N ₂ O ₂
304107	H	cyclopropyl-CH2CH2	F	F	N	C ₁₈ H ₁₆ F ₄ N ₂
304108	H	OPr	F	Cl	N(O)	C ₁₈ H ₁₄ ClF ₃ N ₂ O ₂
304109	H	i-BuO	Me	Cl	N	C ₁₈ H ₁₉ ClF ₂ N ₂ O
304111	H	i-PrNHCH2	F	Cl	N(O)	C ₁₇ H ₁₇ ClF ₃ N ₃ O

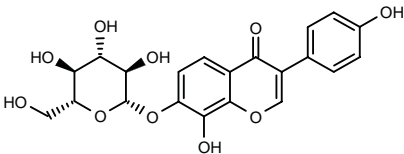
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Johnson, B.L. et al. (DuPont Pharmaceuticals Co.) *Tricyclic cpds. useful as HIV reverse transcriptase inhibitors*. WO 0129037.

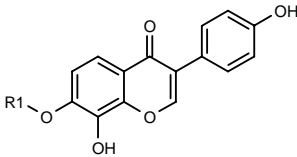
305083

8-Hydroxy-3-(4-hydroxyphenyl)-4-oxo-4*H*-1-benzopyran-7-yl β-D-glucopyranoside



C21 H20 O10; Mol wt: 432.3790

ACTION – Inhibitor of α-glucosidase, an analogue of the known compound A-76202, expected to be useful for the treatment of obesity, diabetes and AIDS. Other exem-plified compounds are:



Compound	R1	Formula
305084	α-D-mannopyranosyl	C ₂₁ H ₂₀ O ₁₀
305085	β-D-galactopyranosyl	C ₂₁ H ₂₀ O ₁₀
305086	β-D-allopyranosyl	C ₂₁ H ₂₀ O ₁₀

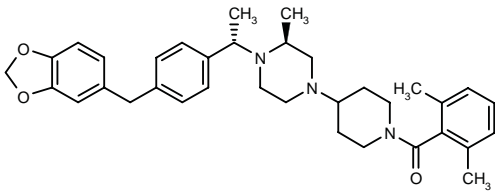
SOURCE – Sankyo.

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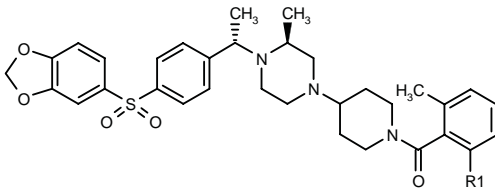
306955

1-[4-[4-[1(*S*)-[4-(1,3-Benzodioxol-5-ylmethyl)phenyl]-ethyl]-3(*S*)-methylpiperazin-1-yl]piperidin-1-yl]-1-(2,6-dimethylphenyl)methanone



C35 H43 N3 O3; Mol wt: 553.7427

ACTION – Anti-HIV-1 agent (IC₅₀ = 8 nM for inhibition of HIV-1 replication in peripheral blood mononuclear cells [PBMCs]) that prevents the entry of HIV-1 into target cells (IC₅₀ = 1.7 nM) via inhibition of binding to chemokine CCR5 receptors (K_i = 18 nM). Compound did not show binding affinity for other chemokine receptors (CCR1, CCR2 and CCR3) and exhibited CCR5-antagonist activity against RANTES-induced calcium flux *in vitro*. Other piperazine-based compounds are:



Compound	R1	Formula
306954	Me	C ₃₄ H ₄₁ N ₃ O ₅ S
307284	NH2	C ₃₃ H ₄₀ N ₄ O ₅ S

SOURCE – Schering-Plough.

REFERENCES

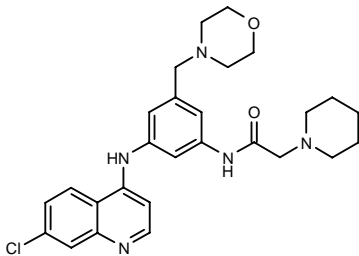
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2. Tagat, J.R. et al. *Piperazine-based CCR5 antagonists as HIV-1 inhibitors. I: 2(S)-Methyl piperazine as a key pharmacophore element*. Bioorg Med Chem Lett 2001, 11(16): 2143.

TREATMENT OF PROTOZOAL DISEASES

306605

N-[3-(7-Chloroquinolin-4-ylamino)-5-(morpholin-4-yl-methyl)phenyl]-2-(1-piperidinyl)acetamide



C27 H32 Cl N5 O2; Mol wt: 494.0358

ACTION – Antimalarial agent active *in vitro* against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* (IC₅₀ = 12.8 and 9.6-12.4 nM, respectively). In a model of *Plasmodium berghei* infection in mice, treatment with compound at a dose of 40 mg/kg p.o. resulted in complete remission of infection.

SOURCES – CNRS; Tibotec.

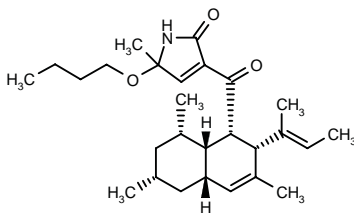
REFERENCES

1. Delareu, S. et al. *Synthesis and in vitro and in vivo antimalarial activity of new 4-anilinoquinolines*. J Med Chem 2001, 44(17): 2827.

ASCOSALIPYRROLIDINONE A

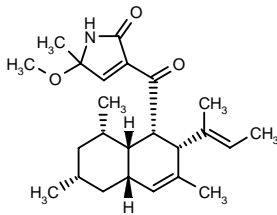
295199

3-[(1*R**,2*S*,4*aS**,6*S**,8*R**,8*aR**)-3,6,8-Trimethyl-2-[1-methyl-1(*E*)-propenyl]-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-ylcarbonyl]-5-butoxy-5-methyl-2,5-dihydro-1*H*-pyrrol-2-one



C27 H41 N O3; Mol wt: 427.6249

ACTION – Antibacterial alkaloid isolated from the obligate marine fungus *Ascochyta salicorniae*, active against *Bacillus megaterium*, *Mycotypha microsporum* and *Microbotryum violaceum*. It also inhibited the growth of two strains of *Plasmodium falciparum* (IC₅₀ = 0.736 and 0.378 µg/ml) and showed significant activity against *Trypanosoma cruzi* and *Trypanosoma rhodesiense* (MIC = 1.1 and 30 µg/ml, respectively).



Ascosalipyrrolidinone B [307767]: C24 H35 N O3

SOURCE – Bayer.

REFERENCES

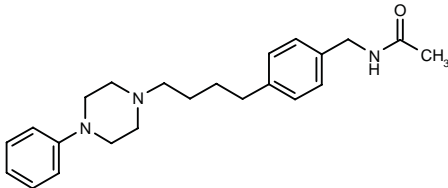
1. Stadler, M. et al. (Bayer AG) *Ascosalipyrrolone derivs*. DE 19962933, WO 0147881.
2. Osterhage, C. et al. *Ascosalipyrrolidinone A, an antimicrobial alkaloid, from the obligate marine fungus Ascochyta salicorniae*. J Org Chem 2000, 65(20): 6412.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

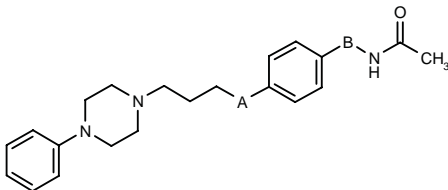
303648

N-[4-[4-(4-Phenylpiperazin-1-yl)butyl]benzyl]acetamide



C23 H31 N3 O; Mol wt: 365.5179

ACTION – Cytokine regulator that is able to suppress TNF-α production and enhance IL-10 production, as demonstrated in lipopolysaccharide-stimulated mice at 10 mg/kg p.o. Potentially useful for the treatment of chronic and acute inflammatory disorders, infection-induced inflammatory disorders, autoimmune diseases, allergic diseases and other TNF-α-mediated conditions. Other exemplified compounds from this series of piperazine derivatives include the following:

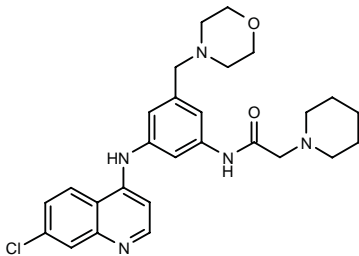


Compound	A	B	Formula
303649	-CH2-	bond	C ₂₂ H ₂₉ N ₃ O
303650	-O-	-CH2-	C ₂₂ H ₂₉ N ₃ O ₂

TREATMENT OF PROTOZOAL DISEASES

306605

N-[3-(7-Chloroquinolin-4-ylamino)-5-(morpholin-4-yl-methyl)phenyl]-2-(1-piperidinyl)acetamide



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ACTION – Antimalarial agent active *in vitro* against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* (IC₅₀ = 12.8 and 9.6-12.4 nM, respectively). In a model of *Plasmodium berghei* infection in mice, treatment with compound at a dose of 40 mg/kg p.o. resulted in complete remission of infection.

SOURCES – CNRS; Tibotec.

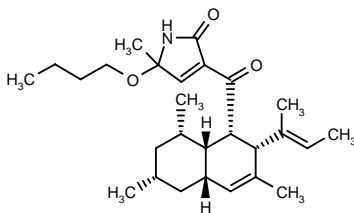
REFERENCES

1. Delareu, S. et al. *Synthesis and in vitro and in vivo antimalarial activity of new 4-anilinoquinolines*. J Med Chem 2001, 44(17): 2827.

ASCOSALIPYRROLIDINONE A

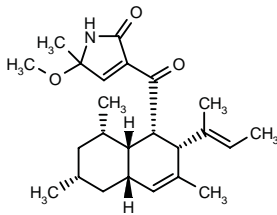
295199

3-[(1*R**,2*S*,4*aS**,6*S**,8*R**,8*aR**)-3,6,8-Trimethyl-2-[1-methyl-1(*E*)-propenyl]-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-ylcarbonyl]-5-butoxy-5-methyl-2,5-dihydro-1*H*-pyrrol-2-one



C27 H41 N O3; Mol wt: 427.6249

ACTION – Antibacterial alkaloid isolated from the obligate marine fungus *Ascochyta salicorniae*, active against *Bacillus megaterium*, *Mycotypha microsporum* and *Microbotryum violaceum*. It also inhibited the growth of two strains of *Plasmodium falciparum* (IC₅₀ = 0.736 and 0.378 µg/ml) and showed significant activity against *Trypanosoma cruzi* and *Trypanosoma rhodesiense* (MIC = 1.1 and 30 µg/ml, respectively).



Ascosalipyrrolidinone B [307767]: C24 H35 N O3

SOURCE – Bayer.

REFERENCES

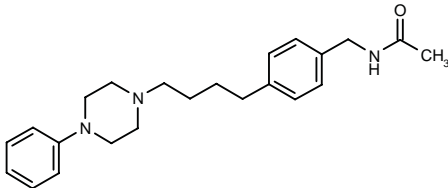
1. Stadler, M. et al. (Bayer AG) *Ascosalipyrrolone derivs*. DE 19962933, WO 0147881.
2. Osterhage, C. et al. *Ascosalipyrrolidinone A, an antimicrobial alkaloid, from the obligate marine fungus Ascochyta salicorniae*. J Org Chem 2000, 65(20): 6412.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

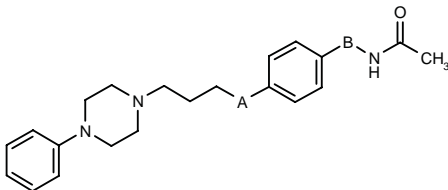
303648

N-[4-[4-(4-Phenylpiperazin-1-yl)butyl]benzyl]acetamide



C23 H31 N3 O; Mol wt: 365.5179

ACTION – Cytokine regulator that is able to suppress TNF-α production and enhance IL-10 production, as demonstrated in lipopolysaccharide-stimulated mice at 10 mg/kg p.o. Potentially useful for the treatment of chronic and acute inflammatory disorders, infection-induced inflammatory disorders, autoimmune diseases, allergic diseases and other TNF-α-mediated conditions. Other exemplified compounds from this series of piperazine derivatives include the following:



Compound	A	B	Formula
303649	-CH2-	bond	C ₂₂ H ₂₉ N ₃ O
303650	-O-	-CH2-	C ₂₂ H ₂₉ N ₃ O ₂

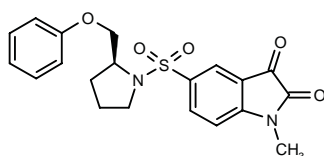
SOURCE – Welfide.

REFERENCES

1. Adachi, K. et al. (Welfide Corp.) *TNF- α production inhibitors and/or IL-10 production promoters*. JP 2001072660.

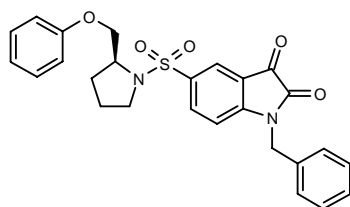
303666¹⁻⁴

1-Methyl-5-[2(S)-(phenoxymethyl)pyrrolidin-1-ylsulfonyl]-1H-indole-2,3-dione



C20 H20 N2 O5 S; Mol wt: 400.4530

ACTION – Nonpeptide inhibitor of caspase 3 and 7 (K_i = 15-30 and 47 nM, respectively) with > 1,000-fold selectivity over caspase 2, 4, 6 and 8 and > 20-fold selectivity over caspase 9. Compound inhibited apoptosis in three cell-based models including human Jurkat T-cells, human chondrocytes and mouse bone marrow neutrophils. Potentially useful for the treatment of osteoarthritis. Another related compound is:



303665^{1,2,4} C26 H24 N2 O5 S

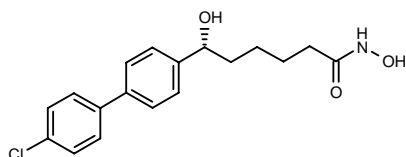
SOURCE – GlaxoSmithKline.

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1. Lee, D. and Long, S.A. (SmithKline Beecham Corp.) *Caspases and apoptosis*. EP 1001933, WO 9906367.
2. Lee, D. et al. (SmithKline Beecham Corp.) *Caspases and apoptosis*. WO 0122966.
3. Lee, D. et al. *Potent and selective nonpeptide inhibitors of caspases 3 and 7 inhibit apoptosis and maintain cell functionality*. J Biol Chem 2000, 275(21): 16007.
4. Lee, D. et al. *Potent and selective nonpeptide inhibitors of caspases 3 and 7*. J Med Chem 2001, 44(12): 2015.

303719

6(R)-(4'-Chlorobiphenyl-4-yl)-6-hydroxyhexanehydroxamic acid



C18 H20 Cl N O3; Mol wt: 333.8130

ACTION – IL-6 production inhibitor found to inhibit TNF- α -stimulated IL-6 production in human lung carcinoma A549 cells (IC_{50} = 0.052 μ M), as well as in IL-1 β -stimulated human synovial cells (IC_{50} = 0.041 μ M). When tested in a collagen-induced arthritis model in rats, compound completely inhibited the development of arthritis at a dose of 10 mg/kg/day p.o. b.i.d. x 28 days and it improved arthritis score by about 60% when given at a dose of 3 mg/kg/day p.o. b.i.d. x 28 days. Potentially useful in the treatment or prevention of inflammatory disorders, sepsis, multiple myeloma, plasma cell leukemia, renal cell cancer, Kaposi's sarcoma, osteoporosis, cachexia, psoriasis, nephritis, hypergammaglobulinemia, diabetes, autoimmune diseases, hepatitis, inflammatory bowel disease, graft-versus-host disease and endometriosis. A representative compound from a series of hydroxamic acid derivatives.

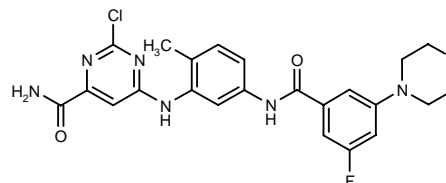
SOURCE – Ono.

REFERENCES

1. Konno, M. et al. (Ono Pharmaceutical Co., Ltd.) *Hydroxamic acid derivs., process for the production thereof and drugs containing the same as the active ingredient*. WO 0121583.

303743

2-Chloro-6-[5-[3-fluoro-5-(4-morpholinyl)benzamido]-2-methylphenylamino]pyrimidine-4-carboxamide



C23 H22 Cl F N6 O3; Mol wt: 484.9168

ACTION – An inhibitor of the production of cytokines such as TNF- α , IL-1, IL-6 and IL-8 that acts via inhibition of p38 kinase activity (IC_{50} ~ 0.03 μ M against p38 α). Compound was shown to inhibit lipopolysaccharide-stimulated TNF- α production in human whole blood with an IC_{50} of approximately 16 μ M. Potentially useful in the treatment of cytokine-mediated disorders such as rheumatoid arthritis, osteoarthritis, gout, inflammatory bowel disease, gastritis, psoriasis, eczema, dermatitis, asthma, bronchitis, allergic rhinitis, adult respiratory distress syndrome, chronic obstructive pulmonary disease, as well as various cardiovascular and cerebrovascular disorders, Alzheimer's disease and osteoporosis. A representative compound from a series of pyrimidine derivatives.

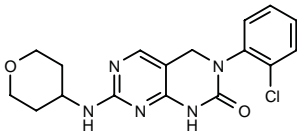
SOURCE – AstraZeneca.

REFERENCES

1. Cumming, J.G. (AstraZeneca AB; AstraZeneca plc) *Pyrimidine derivs*. WO 0127089.

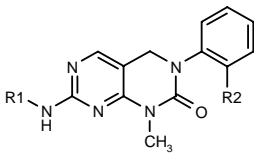
304180

3-(2-Chlorophenyl)-7-(tetrahydropyran-4-ylamino)-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-2-one



C17 H18 Cl N5 O2; Mol wt: 359.8152

ACTION – An inhibitor of p38 kinase reported to be devoid of activity against the T-cell tyrosine kinase p56^{lck} at concentrations below 10 μM. Potentially useful for the treatment or prevention of diseases mediated by proinflammatory cytokines such as TNF and IL-1 including arthritis, Crohn’s disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease, osteoporosis and Alzheimer’s disease. Other specifically claimed compounds from this series of tetrahydropyrimido[4,5-*d*]pyrimidin-2-one deriva-



Compound	R1	R2	Formula
304181	1-(OHCH2CH2)-4-Pip	Me	C ₂₁ H ₂₈ N ₆ O ₂
304182	trans-4-MeO-cyclohexyl-CH2	Cl	C ₂₁ H ₂₆ ClN ₅ O ₂
304183	4-oxo-cyclohexyl	Cl	C ₁₉ H ₂₀ ClN ₅ O ₂

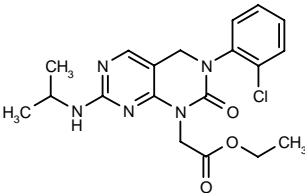
SOURCE – Roche.

REFERENCES

1. Dunn, J.P. et al. (F. Hoffmann-La Roche AG) *Heteroalkylamino-substd. bicyclic nitrogen heterocycles as inhibitors of p38 protein kinase*. WO 0129042.

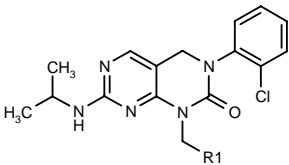
304185

2-[3-(2-Chlorophenyl)-7-(isopropylamino)-2-oxo-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-1-yl]acetic acid ethyl ester



C19 H22 Cl N5 O3; Mol wt: 403.8678

ACTION – An inhibitor of p38 kinase reported to be devoid of activity against the T-cell tyrosine kinase p56^{lck} at concentrations below 10 μM. Potentially useful for the treatment or prevention of diseases mediated by proinflammatory cytokines such as TNF and IL-1 including arthritis, Crohn’s disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease, osteoporosis and Alzheimer’s disease. Other specifically claimed compounds from this series of tetrahydropyrimido[4,5-*d*]pyrimidin-2-one deriva-



Compound	R1	Formula
304186	CO2H	C ₁₇ H ₁₆ ClN ₅ O ₃
304187	CH2OMe	C ₁₈ H ₂₂ ClN ₅ O ₂
304188	CH2SO2Me	C ₁₈ H ₂₂ ClN ₅ O ₃ S
304189	CH2OH	C ₁₇ H ₂₀ ClN ₅ O ₂
304190	(S)-CH(OH)CH2OH	C ₁₈ H ₂₂ ClN ₅ O ₃
304191	(R)-CH(OH)CH2OH	C ₁₈ H ₂₂ ClN ₅ O ₃
304192	1-Pip-CH2	C ₂₂ H ₂₉ ClN ₅ O

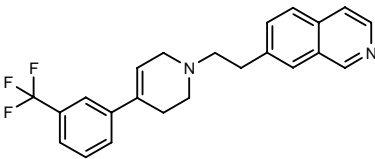
SOURCE – Roche.

REFERENCES

1. Dunn, J.P. et al. (F. Hoffmann-La Roche AG) *Alkylamino subst. bicyclic nitrogen heterocycles as inhibitors of p38 protein kinase*. WO 0129041.

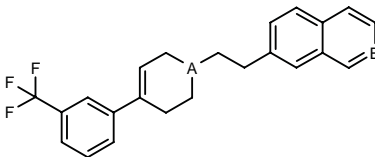
304226

7-[2-[4-[3-(Trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]isoquinoline



C23 H21 F3 N2; Mol wt: 382.4269

ACTION – An inhibitor of TNF-α production reported to exhibit low toxicity, with potential as an analgesic agent and for the treatment of immune and inflammatory disorders. Other specifically claimed compounds from this series of phenyl- and pyridyl-tetrahydropyridines are:



Compound	A	B	Formula
304299	N	N(O)	C ₂₃ H ₂₁ F ₃ N ₂ O
304300	N(O)	N	C ₂₃ H ₂₁ F ₃ N ₂ O
304301	N(O)	N(O)	C ₂₃ H ₂₁ F ₃ N ₂ O ₂

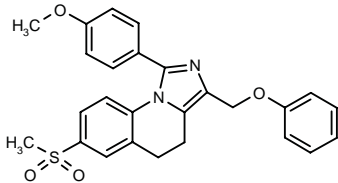
SOURCE – Sanofi-Synthélabo.

REFERENCES

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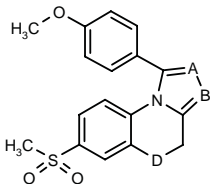
304334

1-(4-Methoxyphenyl)-7-(methylsulfonyl)-3-(phenoxy-methyl)-4,5-dihydroimidazo[1,5-a]quinoline



C26 H24 N2 O4 S; Mol wt: 460.5516

ACTION – Antiinflammatory agent, a selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.16 and > 100 μM, respectively, against COX-2 and COX-1; selectivity index > 625). A representative compound from a series of tricyclic fused imidazole derivatives, wherein the following are also included:



Compound	A	B	D	Formula
304336	C(Me)	N	CH2	C ₂₀ H ₂₀ N ₂ O ₃ S
304337	C(Cl)	N	CH2	C ₁₉ H ₁₇ ClN ₂ O ₃ S
304338	N	C(Br)	CH2	C ₁₉ H ₁₇ BrN ₂ O ₃ S
304339	N	C(CF3)	O	C ₁₉ H ₁₅ F ₃ N ₂ O ₄ S
304340	N	C(CH2OCH2Ph)	O	C ₂₆ H ₂₄ N ₂ O ₅ S

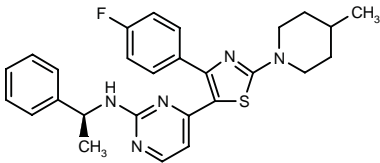
SOURCE – Yakult Honsha.

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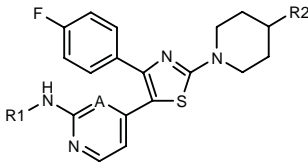
304563

4-[4-(4-Fluorophenyl)-2-(4-methylpiperidin-1-yl)thiazol-5-yl]-N-[1(S)-phenylethyl]pyrimidin-2-amine



C27 H28 F N5 S; Mol wt: 473.6172

ACTION – Inhibitor of p38 MAP kinase that inhibits the production of cytokines such as TNF-α and IL-1 and is thus useful for the treatment of inflammatory disorders, autoimmune diseases, severe infections, transplant rejection and graft-versus-host disease. Other specifically claimed compounds from this series of thiazole and imidazo[4,5-b]pyridine derivatives include the following:



Compound	R1	R2	A	Formula
304564	(S)-CH(Me)Ph	NH2	N	C ₂₆ H ₂₇ FN ₆ S
304565	cyclopropyl-CH2	Me	CH	C ₂₄ H ₂₇ FN ₄ S
304566	(S)-CH(Me)Ph	NH2	CH	C ₂₇ H ₂₈ FN ₅ S

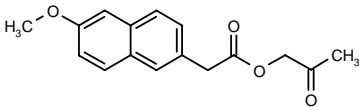
SOURCE – Novartis.

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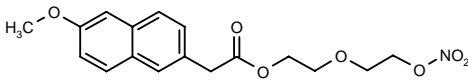
304567

2-(6-Methoxynaphthalen-2-yl)acetic acid 2-oxopropyl ester



C16 H16 O4; Mol wt: 272.2984

ACTION – A representative compound from a series of prodrugs of 6-methoxy-2-naphthylacetic acid (6-MNA), the active metabolite of nabumetone, reported to be more readily transformed to 6-MNA than nabumetone. Compound was found to be transformed to 6-MNA *in vitro* in rat plasma (21% conversion in 2 h) and was shown to be equipotent to nabumetone in a rat paw edema model (ED₅₀ = 33.9 mg/kg vs. 35.9 mg/kg). Another exemplified compound is:



304568: C17 H19 N O7

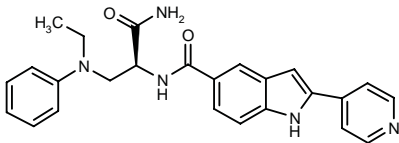
SOURCE – Nobex.

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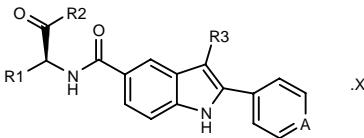
304611

N-[1(S)-Carbamoyl-2-(N-ethyl-N-phenylamino)ethyl]-2-(4-pyridyl)-1H-indole-5-carboxamide



C25 H25 N5 O2; Mol wt: 427.5055

ACTION – A specific inhibitor of IκB kinase (IC₅₀ = 1.0 μM) that is devoid of inhibitory activity against protein kinase A, protein kinase C and casein kinase II at 100 μM. Compound is expected to be useful for the treatment or prevention of diseases involving increased NF-κB activity such as rheumatoid arthritis, osteoarthritis, asthma, myocardial infarction, Alzheimer's disease, cancer and atherosclerosis. Other exemplified substituted indoles are:



Compound	R1	R2	R3	A	X	Formula
304612	CH2CH2Ph	NH2	Ph	CH		C ₃₁ H ₂₇ N ₃ O ₂
304613	CH2CH2Ph	NH2	H	N		C ₂₄ H ₂₂ N ₄ O ₂
304614	CH2SPh	NH2	H	N		C ₂₃ H ₂₀ N ₄ O ₂ S
304615	SCH2Ph	OH	H	N		C ₂₃ H ₁₉ N ₃ O ₃ S
304616	SCH2Ph	OH	Me	N		C ₂₄ H ₂₁ N ₃ O ₃ S
304617	SCH2Ph	NH2	Me	N		C ₂₄ H ₂₂ N ₄ O ₂ S
304619	1-pyrrolyl- -CH2CH2	NH2	Me	N	CF3CO2H	C ₂₃ H ₂₃ N ₅ O .C ₂ HF ₃ O ₂

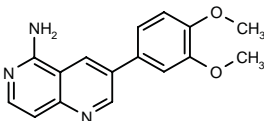
SOURCE – Aventis Pharma.

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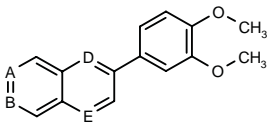
304638

3-(3,4-Dimethoxyphenyl)-1,6-naphthyridin-5-amine



C16 H15 N3 O2; Mol wt: 281.3135

ACTION – An inhibitor of matrix metalloproteinases such as stromelysin 1 (MMP-3; IC₅₀ = 0.16 μg/ml in human arthrosis-derived synovial cells) and of TNF-α production (IC₅₀ = 0.3 μg/ml using lipopolysaccharide-stimulated murine peritoneal cells), potentially useful for the treatment of rheumatoid arthritis, arthrosis, allergic diseases, psoriasis, transplant rejection, arteriosclerosis, ischemia–reperfusion injury, diabetic kidney and ocular diseases, cancer, glomerulonephritis, infectious diseases, inflammatory bowel disease and hepatitis. Other exemplified compounds from this series of polyaza-naphthalene derivatives include the following:



Compound	A	B	D	E	Formula
304640	N	CH	CH	N	C ₁₆ H ₁₄ N ₂ O ₂
304641	N	C(NH2)	CH	N	C ₁₆ H ₁₅ N ₃ O ₂
304642	CH	N	CH	N	C ₁₆ H ₁₄ N ₂ O ₂
304643	CH	N	N	CH	C ₁₆ H ₁₄ N ₂ O ₂

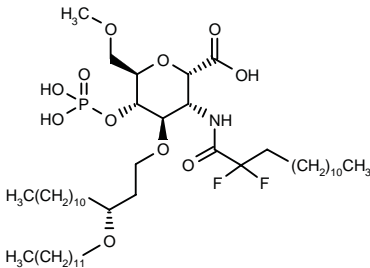
SOURCE – Ajinomoto.

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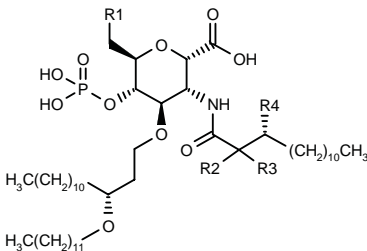
304644

2,6-Anhydro-3-deoxy-3-(2,2-difluorotetradecanamido)-4-O-[3(R)-(dodecyloxy)tetradecyl]-7-O-methyl-5-O-phosphono-D-glycero-D-ido-heptonic acid



C48 H92 F2 N O11 P; Mol wt: 928.2208

ACTION – Agent for the treatment of inflammatory and autoimmune diseases and septicemia with excellent macrophage depressant activity. *In vitro*, compound inhibited lipopolysaccharide-stimulated TNF-α production in TPA-treated human monocytic U-937 cells with an IC₅₀ value of 1.5 nM, while exhibiting no cytotoxicity against U-937 cells at concentrations up to 5 μM. Other exemplified compounds from this series of ether-type GLA-60 analogues include the following:



Compound	R1	R2=R3	R4	Formula
304646	OH	H	OH	C ₄₇ H ₉₂ NO ₁₂ P
304647	OMe	H	OH	C ₄₈ H ₉₄ NO ₁₂ P
304648	F	H	OH	C ₄₇ H ₉₁ FNO ₁₁ P
304649	OMe	H	H	C ₄₈ H ₉₄ NO ₁₁ P
304670	OH	H	H	C ₄₇ H ₉₂ NO ₁₁ P
304671	F	F	H	C ₄₇ H ₈₉ F ₃ NO ₁₀ P

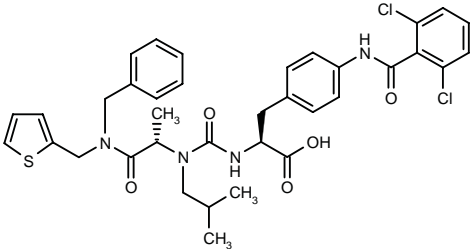
SOURCE – Sankyo.

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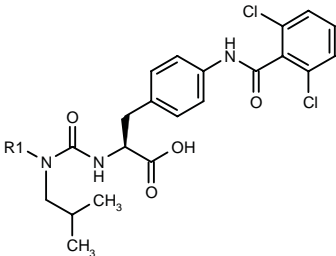
304658

N-[*N*-[1(*S*)-[*N*-Benzyl-*N*-(thien-2-ylmethyl)carbamoyl]-ethyl]-*N*-isobutylcarbamoyl]-4-(2,6-dichlorobenzamido)-*L*-phenylalanine



C36 H38 Cl2 N4 O5 S; Mol wt: 709.6912

ACTION – VLA-4 antagonist proven to inhibit the adhesion of HL-60 cells to human VCAM-1-expressing CHO cells with an IC₅₀ value of 0.01 nM. Potentially useful for the treatment or prevention of VLA-4-mediated conditions such as rheumatoid arthritis, asthma, allergy, nephritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, cardiovascular disorders, arteriosclerosis, diabetes, cancer and transplant rejection. Other exemplified compounds from this series of urea derivatives include the following:



Compound	R1	Formula
304659	4-Cl-PhCH(Me)	C ₂₉ H ₃₀ Cl ₃ N ₃ O ₄
304660	4-Pyr-CH(Me)	C ₂₈ H ₃₀ Cl ₂ N ₄ O ₄
304661	2-thiazolyl-CH(Me)	C ₂₆ H ₂₈ Cl ₂ N ₄ O ₄ S
304662	4,5,6,7-tetrahydro-4-benzothienyl	C ₂₉ H ₃₁ Cl ₂ N ₃ O ₄ S
304663	3,4-(MeO)2-PhCH2CH2	C ₃₁ H ₃₆ Cl ₂ N ₃ O ₆
304664	(<i>S</i>)-CH(Me)CON(Et)2	C ₂₈ H ₃₆ Cl ₂ N ₄ O ₅
304665	(<i>S</i>)- <i>i</i> -BuN(Me)COCH(Me)	C ₂₉ H ₃₈ Cl ₂ N ₄ O ₅
304666	(<i>S</i>)-CH(Me)CON(<i>i</i> -Bu)2	C ₃₂ H ₄₄ Cl ₂ N ₄ O ₅

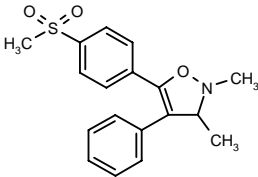
SOURCE – Kaken.

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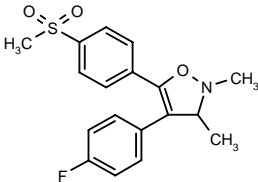
307249

2,3-Dimethyl-5-[4-(methylsulfonyl)phenyl]-4-phenyl-2,3-dihydroisoxazole



C18 H19 N O3 S; Mol wt: 329.4181

ACTION – Cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.0042 μM) with a high COX-1/COX-2 selectivity index (SI = 61,454) and excellent antiinflammatory activity in the carrageenan-induced paw edema model in rats (ED₅₀ = 44 mg/kg p.o.), as well as analgesic activity in the NaCl-induced abdominal constriction assay in mice. Potentially useful for the treatment of inflammatory diseases and pain. Another 4,5-diphenyl-4-isoxazoline is:



307250: C18 H18 F N O3 S

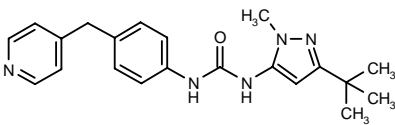
SOURCE – University of Alberta, Edmonton, AB (CA).

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307747

N-(3-*tert*-Butyl-1-methyl-1*H*-pyrazol-5-yl)-*N*'-[4-(pyridin-4-ylmethyl)phenyl]urea



C21 H25 N5 O; Mol wt: 363.4625

ACTION – Potent and selective p38 MAP kinase inhibitor (IC₅₀ = 42 nM) with no activity against a range of other kinases, except for p38β1 (IC₅₀ = 110 nM). Compound significantly inhibited lipopolysaccharide-induced TNF-α production (86.5% inhibition at 50 mg/kg p.o.) and TNF-α-induced IL-6 production (84% inhibition at 50 mg/kg p.o.) in mice. Moreover, in a chronic collagen-induced arthritis model in mice, a dose of 30 mg/kg p.o. produced significant improvement in terms of clinical severity scores, interstitial edema and inflammatory cell infiltration. Potentially useful for the treatment of arthritis.

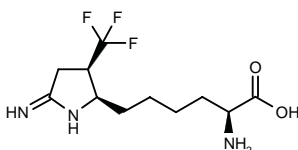
SOURCE – Bayer.

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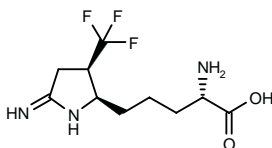
307751

6-[5-Imino-3(*R*)-(trifluoromethyl)pyrrolidin-2(*R*)-yl]-L-nor-leucine



C11 H18 F3 N3 O2; Mol wt: 281.2762

ACTION – Nitric oxide synthase (NOS) inhibitor selective for the human inducible isoform over the human endothelial and neuronal isoforms (IC_{50} = 0.8, 39 and 3.4 μ M, respectively). Compound inhibited lipopolysaccharide-induced NO production in rats with an ED_{50} of 0.5 mg/kg. Potentially useful as an antiinflammatory agent. Another related compound is:



307750: C10 H16 F3 N3 O2

SOURCE – Pharmacia.

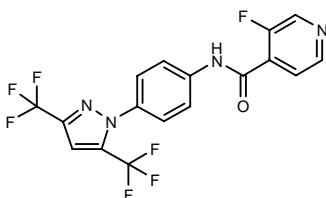
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A-285354.0*

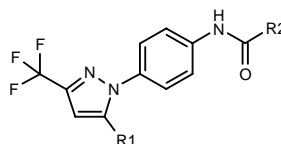
281798

N-[4-[3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]-3-fluoropyridine-4-carboxamide



C17 H9 F7 N4 O; Mol wt: 418.2711

ACTION – Cytokine production inhibitor shown to be 10-fold more potent than ciclosporin against IL-2 production in an *ex vivo* assay; compound was also able to inhibit the production of IL-4, IL-5, IL-8 and eotaxin. Unlike ciclosporin and FK-506, compound inhibited NFAT translocation without directly inhibiting calcineurin-mediated NFAT dephosphorylation. Potentially useful for the treatment of inflammatory diseases and as an immunomodulator. Other bis(trifluoromethyl)pyrazoles are:



Compound	R1	R2	Formula
A-160726.0 [307208]	CF3	1,2,3-thiadiazol-5-yl	C ₁₅ H ₉ F ₆ N ₆ OS
A-278644.0 [307209]	4-Pyr	3-F-4-Pyr	C ₂₁ H ₁₃ F ₄ N ₅ O
A-292856.0 [307210]	2-furyl	3-F-4-Pyr	C ₂₀ H ₁₂ F ₄ N ₄ O ₂

SOURCES – Abbott; Millennium.

REFERENCES

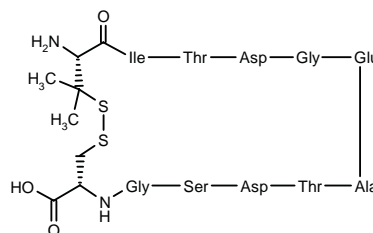
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*Identified compound **281798** Drug Data Rep 2000, 022(01): 0077.

cLAB.L

295967

L-Penicillaminyl-L-isoleucyl-L-threonyl-L-aspartyl-glycyl-L-glutamyl-L-alanyl-L-threonyl-L-aspartyl-L-seryl-glycyl-L-cysteine *S*-3.1-*S*-3.12-disulfide



C45 H72 N12 O22 S2; Mol wt: 1197.2580

ACTION – Cyclic peptide derived from the I-domain of the α -subunit of LFA-1 (lymphocyte function-associated antigen-1), proven to inhibit the LFA-1/ICAM-1 (intracellular adhesion molecule-1) interaction via direct binding to the D1 domain of ICAM-1 on activated T-cells. This resulted in inhibition of the adherence of T-cells to epithelial cell monolayers. Potentially useful for the treatment of inflammatory and autoimmune diseases.

SOURCE – University of Kansas, Lawrence, KS (US).

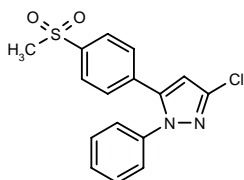
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FR-188582

306772

3-Chloro-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1*H*-pyrazole



C16 H13 Cl N2 O2 S; Mol wt: 332.8097

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; $IC_{50} = 0.017 \mu M$) with > 6,000-fold selectivity over COX-1. In rats with adjuvant-induced arthritis, compound suppressed paw edema ($ED_{50} = 0.074$ and 0.063 mg/kg p.o. in adjuvant-injected paw and contralateral paw, respectively) and reduced the formation of immunoreactive PGE_2 ($ED_{50} = 0.11$ and 0.068 mg/kg p.o., respectively) but not LTB_4 in arthritic paws. Moreover, compound did not induce gastric lesions in rats at doses up to 32 mg/kg p.o. and it did not inhibit the levels of immunoreactives PGE_2 and 6-keto- $PGF_{1\alpha}$ in rat gastric mucosa.

SOURCE – Fujisawa.

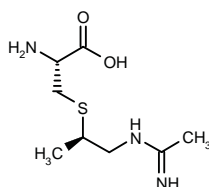
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GW-432042*

284029

S-[2-(1-Iminoethylamino)-1(*R*)-methylethyl]-L-cysteine



C8 H17 N3 O2 S; Mol wt: 292.2291

ACTION – Potent inhibitor of inducible nitric oxide synthase (iNOS) with an IC_{50} value of $1.1 \mu M$ for inhibition of purified human iNOS and of $0.26 \mu M$ for inhibition of enzyme activity in rat aortic rings. Compound exhibited high selectivity over neuronal NOS (nNOS; $IC_{50} = 64 \mu M$) and endothelial NOS (eNOS; $IC_{50} = 150 \mu M$) and high tissue selectivity, being inactive in rat brain slices. Potentially useful for the treatment of inflammatory diseases.

SOURCE – GlaxoSmithKline.

REFERENCES

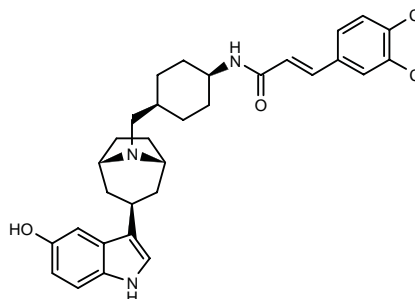
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*Identified compound **284029** Drug Data Rep 2000, 022(02): 0177.

SB-380732

306348

cis-3-(3,4-Dichlorophenyl)-*N*-[4-[*exo*-3-(5-hydroxy-1*H*-indol-3-yl)-8-azabicyclo[3.2.1]oct-8-ylmethyl]cyclohexyl]-2-propenamide



C31 H35 Cl2 N3 O2; Mol wt: 552.5425

ACTION – Potent and selective chemokine CCR2B receptor antagonist with nanomolar affinity at CCR2B receptors ($K_i = 40$ nM) and high selectivity over a number of 5-HT and dopamine receptors. Potentially useful for the treatment of rheumatoid arthritis and atherosclerosis.

SOURCE – GlaxoSmithKline.

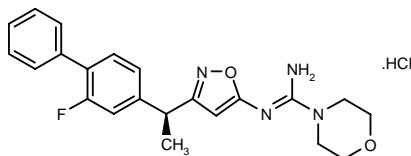
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SMP-114*

270688

*N*²-[3-[1(*S*)-(2-Fluorobiphenyl-4-yl)ethyl]-5-isoxazolyl]-4-morpholinecarboxamide hydrochloride



C₂₂ H₂₃ F N₄ O₂ · HCl; Mol wt: 430.9086

ACTION – Disease-modifying antirheumatic agent proven to inhibit soft tissue swelling and joint destruction in models of rheumatoid arthritis in rats induced by *Mycobacterium butyricum*, adjuvant or collagen. Compound inhibited endotoxin-induced PGE₂ release from mouse macrophage RAW264.5 cells (IC₅₀ = 5.28 μM) but was inactive against cyclooxygenases (COX-1 and COX-2; IC₅₀ > 100 μM). It showed antiproliferative activity against mouse fibroblast L929 cells stimulated by basic fibroblast growth factor (bFGF; IC₅₀ = 1.05 μM), inhibited spontaneous osteoclast formation from inflammatory cells derived from knee joints of arthritic mice, and suppressed T-lymphocyte activation. Compound is undergoing phase I trials for the treatment of rheumatoid arthritis.

SOURCE – Sumitomo Pharmaceuticals.

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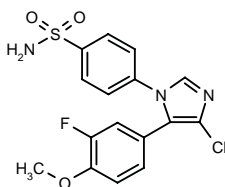
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*Identified compound **270688** (see **270684**) Drug Data Rep 1999, 021(01): 0070.

UR-8880

293295

4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)-1*H*-imidazol-1-yl]benzenesulfonamide



C₁₆ H₁₃ Cl F N₃ O₃ S; Mol wt: 381.8137

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor with IC₅₀ values in human whole blood and human osteosarcoma cells of 66.9 nM and 5.6 nM, respectively, and no significant effect against COX-1 in U-937 cells (IC₅₀ = 0.006 and 3.3 μM against COX-2 and COX-1, respectively). It displayed high efficacy in several inflammation models in rats including carrageenan-induced paw edema and hyperalgesia (ID₂₅ = 3.8 and 0.23 mg/kg p.o., respectively), the air pouch model (ID₅₀ = 0.24 mg/kg p.o. for inhibition of PGE₂ production) and adjuvant-induced arthritis (ID₅₀ = 0.18 mg/kg/day p.o.), where compound improved arthritic index, radiographic score and prevented body weight decrease. Compound showed excellent gastric tolerance: when given at the dose of 100 mg/kg b.i.d. for 4 days it did not produce ⁵¹C excretion in rats; it did not reduce PGE₂ levels in rat stomach and did not induce gastric macroscopic damage after 14 days' treatment at a dose of 50 mg/kg. Moreover, UR-8880 did not inhibit cytochrome P-450 CYP3A4, did not induce *in vitro* toxicity and exhibited a good pharmacokinetic profile, with oral availability of 53 and 81% in rats and dogs, respectively.

SOURCE – Uriach.

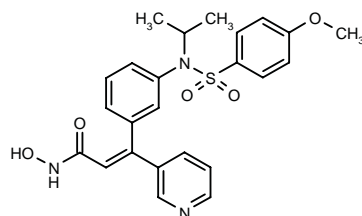
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1. Almansa, C. et al. (J. Uriach & Cia., SA) *Novel imidazoles with anti-inflammatory activity.* EP 1122243, WO 0023426.
2. Almansa, C.e et al. *Discovery of UR-8880: A new COX-2 selective inhibitor.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 267.
3. Gómez-Casajús, L.A. et al. *New imidazole derivatives as potent, selective and orally active cyclooxygenase 2 inhibitors.* Methods Find Exp Clin Pharmacol 2000, 22(6): Abst CO-15.
4. Gómez-Casajús, L.A. et al. *UR-8880, a new imidazole derivative as potent, selective and orally active COX-2 inhibitor.* Inflamm Res 2001, 50(Suppl. 3): Abst W17/02.
5. Ramis, I. et al. *The gastrointestinal safety profile of UR-8880, a new cyclooxygenase-2 inhibitor.* Inflamm Res 2001, 50(Suppl. 3): Abst 066.

W-3646

307743

3-[3-[*N*-Isopropyl-*N*-(4-methoxyphenylsulfonyl)amino]-phenyl]-3-(3-pyridyl)-2(*E*)-propenohydroxamic acid



C₂₄ H₂₅ N₃ O₅ S; Mol wt: 467.5435

ACTION – Potent TNF-α-converting enzyme (TACE) inhibitor (IC₅₀ = 3.1 nM) with high selectivity versus matrix metalloproteinases (MMPs), giving IC₅₀ values > 10,000 nM against MMP-1, MMP-2, MMP-8, MMP-9 and MMP-13, and of 190 nM against MMP-3. In mice, compound dose-dependently inhibited lipopolysaccharide-induced TNF-α production with 67% inhibition at a dose of 30 mg/kg p.o. Potentially useful for the treatment of rheumatoid arthritis, sepsis and type 2 diabetes.

SOURCE – Wakunaga.

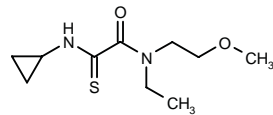
REFERENCES

1. Hirata, T. et al. *Discovery of potent, highly selective, and orally active propenohydroxamate TNF-alpha converting enzyme (TACE) inhibitors*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 262.

IMMUNOMODULATING AGENTS

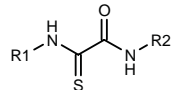
304319

2-(Cyclopropylamino)-N-ethyl-N-(2-methoxyethyl)-2-thioacetamide



C10 H18 N2 O2 S; Mol wt: 230.3302

ACTION – Agent for the treatment of immune and allergic disorders that acts via activation of T-cells and mast cells participating in immunity and allergic reactions, and inhibition of tyrosine phosphatase carried by the CD45 antigen (IC₅₀ = 0.01 μM using CD45 from human leukemia Ball-1 cell membranes). Other exemplified compounds from this series of N-cycloalkyl thiooxamide derivatives include the following:



Compound	R1	R2	Formula
304321	cyclopropyl	4-C7H15-Ph	C ₁₈ H ₂₆ N ₂ OS
304322	cyclobutyl	cyclopentyl	C ₁₁ H ₁₈ N ₂ OS
304323	cyclobutyl	3-MeO-Ph	C ₁₃ H ₁₆ N ₂ O ₂ S
304324	cyclobutyl	3-(PhO)-Ph	C ₁₈ H ₁₈ N ₂ O ₂ S
304325	cyclobutyl	3-Ph-Ph	C ₁₈ H ₁₈ N ₂ OS
304326	cyclobutyl	endo-bicyclo[2.2.1]hept-2-yl	C ₁₃ H ₂₀ N ₂ OS

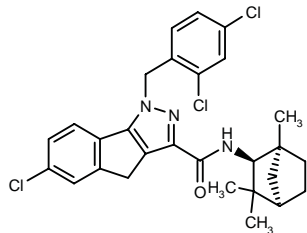
SOURCE – Taisho.

REFERENCES

1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *N-Cycloalkyl thiooxamide derivs*. WO 0128991.

304737

6-Chloro-1-(2,4-dichlorobenzyl)-N-[(1S,2S,4R)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]-1,4-dihydroindeno[1,2-c]-pyrazole-3-carboxamide



C28 H28 Cl3 N3 O; Mol wt: 528.9082

ACTION – Selective cannabinoid CB₂ receptor antagonist, a representative compound from a series of tri-cyclic 1-benzylpyrazole-3-carboxylic acid derivatives. Potentially useful for the treatment of CB₂-mediated disorders, particularly immune and inflammatory disorders.

SOURCE – Sanofi-Synthélabo.

REFERENCES

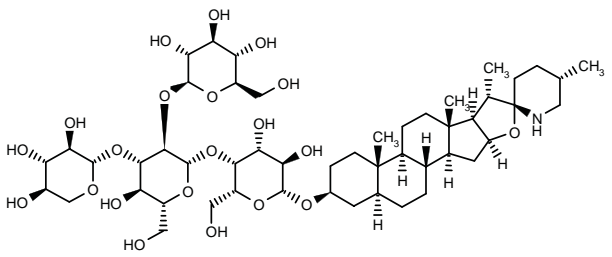
1. Barth, F. et al. (Sanofi-Synthélabo) *1-Benzylpyrazoles-3-carboxylic acid tricyclic derivs. as cannabinoid receptor antagonists*. FR 2800372, WO 0132629.

TOMATINE

306834

(3β,5α,22β,25S)-Spirosolan-3-yl O-β-D-glucopyranosyl-(1→2)-O-[β-D-xylopyranosyl-(1→3)]-O-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside

Lycopersicin



C50 H83 N O21; Mol wt: 1034.1920

ACTION – Alkaloid glycoside derived from leaves of the wild tomato *Lycopersicon pimpinellifolium*, proven to potentiate the cytotoxic T-cell response to a major pre-erythrocytic stage malaria vaccine candidate antigen –a 9-mer– peptide from *Plasmodium berghei* circumsporozoite (CS) protein. Splenocytes derived from mice immunized with tomatine–CS peptide and then restimulated *in vitro* with *P. berghei* CS peptide exhibited significant upregulation of interferon gamma production and a peptide-specific cytolytic T-lymphocyte response, compared to splenocytes from mice immunized with tomatine–saline or from naive controls. In addition, immunization with the tomatine–CS peptide caused a significant delay in the onset of erythrocytic infection after challenge with *P. berghei* sporozoites *in vivo*. Potentially useful as a malaria vaccine adjuvant.

SOURCES – Queen Mary and Westfield College, London (GB); St. Bartholomew and the Royal London School of Medicine and Dentistry, London (GB); University of Southampton, Southampton (GB).

REFERENCES

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3. Rajananthanan, P. et al. *Evaluation of novel aggregate structures as adjuvants: Composition, toxicity studies and humoral responses*. Vaccine 1999, 17(7-8): 715.

SOURCE – Wakunaga.

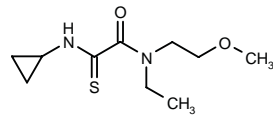
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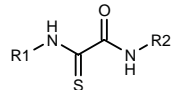
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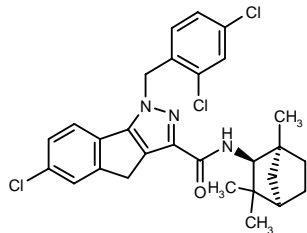
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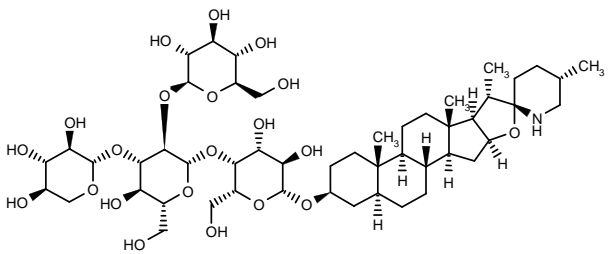
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TOMATINE

306834

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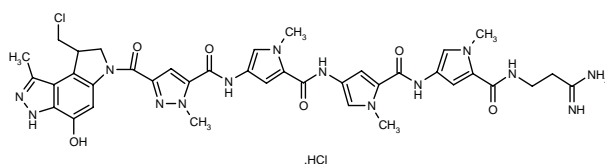
5. Sheikh, N.A. et al. *Generation of antigen specific CD8+ cytotoxic T cells following immunization with soluble protein formulated with novel glycoside adjuvants.* Vaccine 1999, 17(23-24): 2974.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

305868

N-[5-[*N*-[5-[*N*-[5-[*N*-(2-Amidinoethyl)carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]-3-[8-(chloromethyl)-4-hydroxy-1-methyl-3,6,7,8-tetrahydropyrrolo[3,2-*e*]indazol-6-ylcarbonyl]-1-methyl-1*H*-pyrazole-5-carboxamide hydrochloride



C38 H41 Cl N14 O6 . HCl; Mol wt: 825.2869

ACTION – Water-soluble hybrid compound that combines lexitropsin, a polypyrrole minor groove binder structurally related to distamycin A, and a pyrazole analogue of the cyclopropylpyrroloindole (CPI) subunit of the antitumor antibiotic (+)-CC-1065. The hybrid compound showed broad cytotoxic activity against a panel of murine and human tumor cell lines including murine leukemia L1210 and murine mammary carcinoma FM3A cells (IC_{50} = 7.4 and 31 nM, respectively), human leukemia MOLT-4 and CEM cells (IC_{50} = 17 and 71 nM, respectively) and human lymphoma Daudi cells (IC_{50} = 8.8 nM). Compound also inhibited vaccinia virus replication (MIC = 19 ng/ml) at concentrations at least 40-fold below the cytotoxic concentration in E6SM host cells. The cytotoxic activity of this hybrid appeared to be due to its sequence-selective DNA-alkylating activity.

SOURCES – Università di Ferrara, Ferrara (IT); Rega Institute for Medical Research, Leuven (BE); Tokyo Medical and Dental University, Tokyo (JP).

REFERENCES

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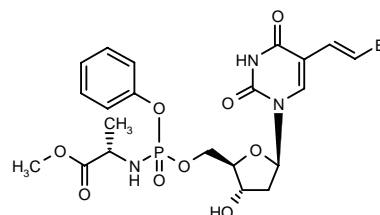
ANTIMETABOLITES

NB-1011

272550

N-[[5-[(*E*)-2-Bromovinyl]-2'-deoxyuridin-5'-*O*-yl]-(phenoxy)phosphoryl]-L-alanine methyl ester

Thymectacin
NB-101



C21 H25 Br N3 O9 P; Mol wt: 574.3185

ACTION – Small-molecule anticancer agent with selectivity for tumor cells expressing high levels of thymidylate synthase (TS). A nucleoside analogue phosphoramidate, it is converted inside cells to bromovinyldeoxyuridine monophosphate (BVdUMP), which binds to the enzyme and is converted by TS to cytotoxic products. Compound was active *in vitro* against high TS-expressing tumor cells such as 5-FU-resistant colon carcinoma H630R10 cells and raltitrexed (Tomudex)-resistant breast adenocarcinoma MCF-7/TDX cells (IC_{50} = 65 and 3 μ M, respectively). Moreover, MCF-7/TDX cells treated with compound exhibited significant increases in mRNA levels of the p53 target genes *p21*, *Bax* and *GADD45*, and an increase in p53, p21 and Bax protein levels. NB-1011-treated cells also accumulated in the G_2/M phase of the cell cycle. *In vivo*, in athymic mice bearing H630R10 or MCF-7/TDX xenografts, compound (1.25-3.5 mg/kg/day i.p. for 14 days) significantly decreased tumor volume compared to vehicle- or Tomudex-treated animals.

SOURCES – Elan; NewBiotics.

REFERENCES

1. Shepard, H.M. (NewBiotics, Inc.) *Enzyme catalyzed therapeutic agents.* JP 2001220397, US 6245750, WO 9937753.

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3. Boyer, C.R. et al. *Nucleoside transport inhibitors, dipyradamole and P-nitrobenzylthionine, selectively potentiate the activity of NB1011 against human tumor cell lines expressing high levels of thymidylate synthase.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1594.

4. Lackey, D.B. et al. *Enzyme-catalyzed therapeutic agent (ECTA) design: Activation of the antitumor ECTA compound NB1011 by thymidylate synthase.* Biochem Pharmacol 2001, 61(2): 179.

5. Li, Q. et al. *A novel approach to thymidylate synthase as a target for cancer chemotherapy.* Mol Pharmacol 2001, 59(3): 446.

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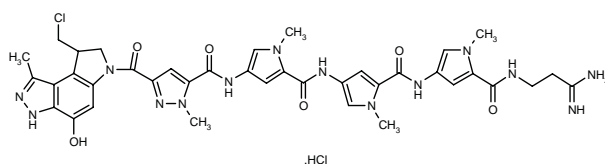
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ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

305868

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ACTION – Water-soluble hybrid compound that combines lexitropsin, a polypyrrole minor groove binder structurally related to distamycin A, and a pyrazole analogue of the cyclopropylpyrroloindole (CPI) subunit of the antitumor antibiotic (+)-CC-1065. The hybrid compound showed broad cytotoxic activity against a panel of murine and human tumor cell lines including murine leukemia L1210 and murine mammary carcinoma FM3A cells (IC_{50} = 7.4 and 31 nM, respectively), human leukemia MOLT-4 and CEM cells (IC_{50} = 17 and 71 nM, respectively) and human lymphoma Daudi cells (IC_{50} = 8.8 nM). Compound also inhibited vaccinia virus replication (MIC = 19 ng/ml) at concentrations at least 40-fold below the cytotoxic concentration in E6SM host cells. The cytotoxic activity of this hybrid appeared to be due to its sequence-selective DNA-alkylating activity.

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ANTIMETABOLITES

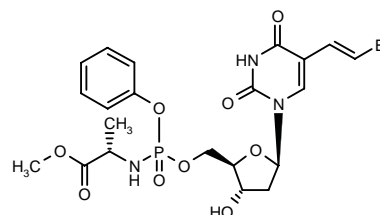
NB-1011

272550

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Thymectacin

NB-101



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ACTION – Small-molecule anticancer agent with selectivity for tumor cells expressing high levels of thymidylate synthase (TS). A nucleoside analogue phosphoramidate, it is converted inside cells to bromovinyldeoxyuridine monophosphate (BVdUMP), which binds to the enzyme and is converted by TS to cytotoxic products. Compound was active *in vitro* against high TS-expressing tumor cells such as 5-FU-resistant colon carcinoma H630R10 cells and raltitrexed (Tomudex)-resistant breast adenocarcinoma MCF-7/TDX cells (IC_{50} = 65 and 3 μ M, respectively). Moreover, MCF-7/TDX cells treated with compound exhibited significant increases in mRNA levels of the p53 target genes *p21*, *Bax* and *GADD45*, and an increase in p53, p21 and Bax protein levels. NB-1011-treated cells also accumulated in the G_2/M phase of the cell cycle. *In vivo*, in athymic mice bearing H630R10 or MCF-7/TDX xenografts, compound (1.25-3.5 mg/kg/day i.p. for 14 days) significantly decreased tumor volume compared to vehicle- or Tomudex-treated animals.

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8. *Company Profile: NewBiotics.* DailyDrugNews.com (Daily Essentials) 1999, Feb 16.

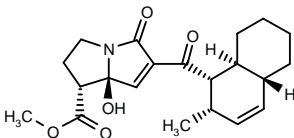
9. *NewBiotics and Elan form joint venture to develop colon cancer therapy.* DailyDrugNews.com (Daily Essentials) 2001, Feb 8.

10. *NewBiotics completes private placement and prepares to advance study of lead product.* DailyDrugNews.com (Daily Essentials) 2000, April 7.

ANTIBIOTICS AND ALKALOIDS

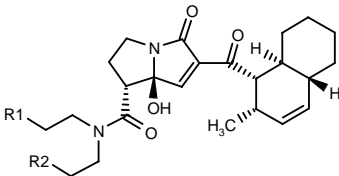
304309

(1*R*,7*aS*)-7*a*-Hydroxy-6-[(1*S*,2*S*,4*aR*,8*aS*)-2-methyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-ylcarbonyl]-5-oxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid methyl ester



C21 H27 N O5; Mol wt: 373.4463

ACTION – Antineoplastic and antibacterial agent with MIC values of 0.52, 1.0 and 0.52 mg/ml, respectively, against *Enterococcus hirae* ATCC 10541, *Staphylococcus aureus* ATCC 6538P and *Bacillus subtilis* ATCC 10707. It also exhibited antiproliferative activity against human renal carcinoma ACHN cells (IC₅₀ = 4.4 μM). Other exemplified compounds from this series of UCS-1025 derivatives include the following:



Compound	R1=R2	Formula
304310	H	C ₂₄ H ₃₄ N ₂ O ₄
304311	Et	C ₂₈ H ₄₂ N ₂ O ₄

SOURCE – Kyowa Hakko.

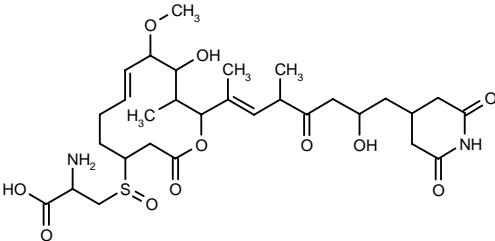
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NK-30424-BS-2

303549

2-Amino-3-[10-hydroxy-12-[7-(2,6-dioxopiperidin-4-yl)-6-hydroxy-1,3-dimethyl-4-oxo-1-heptenyl]-9-methoxy-11-methyl-2-oxooxacyclododec-7-en-4-ylsulfinyl]propionic acid diastereoisomer 1



C30 H46 N2 O11 S; Mol wt: 642.7624

ACTION – An analogue of NK-30424 with antitumor activity (IC₅₀ = 0.06 μM against the proliferation of murine leukemia J774.1 cells) and also shown to inhibit TNF-α production (IC₅₀ = 0.03 μM in lipopolysaccharide-stimulated murine macrophages). Other diastereomers described are **NK-30424-AS-1**, **NK-30424-AS-2** and **NK-30424-BS-1**.

SOURCE – Nippon Kayaku.

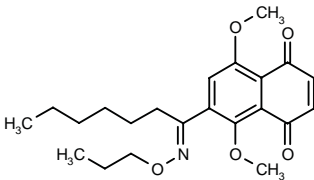
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DNA-INTERCALATING DRUGS

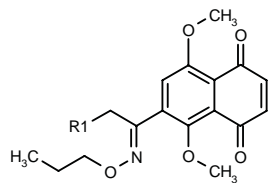
306495

5,8-Dimethoxy-6-[1-(propoxyimino)heptyl]-1,4-naphthoquinone



C22 H29 N O5; Mol wt: 387.4731

ACTION – Antineoplastic agent, an inhibitor of DNA topoisomerase I with antiproliferative activity against murine leukemia L1210 cells and *in vivo* antitumor activity in ICR mice bearing sarcoma 180 cells. Other naphthoquinone derivatives are:



Compound	R1	Formula
306493	H	C ₁₇ H ₁₉ NO ₅
306494	Bu	C ₂₁ H ₂₇ NO ₅
306496	C6H13	C ₂₃ H ₃₁ NO ₅
306497	C7H15	C ₂₄ H ₃₃ NO ₅
306498	C8H17	C ₂₅ H ₃₅ NO ₅
306499	C9H19	C ₂₆ H ₃₇ NO ₅
306500	C11H23	C ₂₈ H ₄₁ NO ₅

SOURCES – Chungnam National University, Taejon (KR); Kuhnil Pharmaceutical.

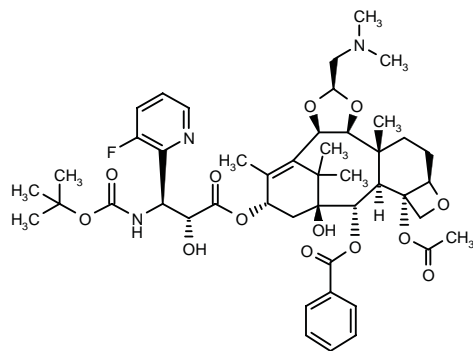
REFERENCES

1. Song, G.Y. et al. *Naphthazarin derivatives (VII): Antitumor action against ICR mice bearing ascitic S-180 cells*. Arch Pharmacol Res 2001, 24(3): 190.

ANTIMITOTIC DRUGS

304277

Benzoic acid (2*a*S,2*b*R,3*S*,4*S*,6*S*,8*a*R,10*S*,11*a*S,11*b*R,13*a*R)-2*a*-acetoxo-6-[3(*S*)-(tert-butoxycarbonylamino)-3-(3-fluoropyridin-2-yl)-2(*R*)-hydroxypropanoyloxy]-10-(dimethylaminomethyl)-4-hydroxy-7,11*b*,14,14-tetramethyl-2*a*,2*b*,3,4,5,6,8*a*,11*a*,11*b*,12,13,13*a*-dodecahydro-4,8-methano-2*H*-oxeto[3'',2'':3',4']benzo[1',2':3,4]-cyclodeca[1,2-*d*][1,3]dioxol-3-yl ester



C46 H60 F N3 O13; Mol wt: 881.9860

ACTION – A representative compound from a series of pentacyclic taxanes with antitumor activity, together with improved toxicity, reduced hepatic metabolism and increased oral bioavailability compared to previously disclosed structurally related taxanes. *In vivo*, compound displayed equipotent antitumor activity when given either i.v. or p.o. to mice bearing s.c.-implanted melanoma B16 at a dose of 7.9 or 11.9 mg/kg. A low rate of metabolism was observed following incubation with human hepatic microsomes. When compound was administered orally to monkeys at a dose of 1.8 mg/kg, a bioavailability of 62.4% was observed.

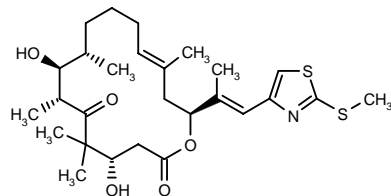
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Soga, T. et al. (Daiichi Pharmaceutical Co., Ltd.) *Pentacyclic taxane cpds*. WO 0127115.

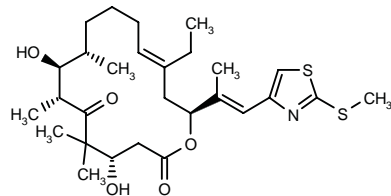
304316

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Dihydroxy-5,5,7,9,14-pentamethyl-16-[(*E*)-1-methyl-2-[2-(methylsulfonyl)thiazol-4-yl]vinyl]oxacyclohexadec-13(*E*)-ene-2,6-dione

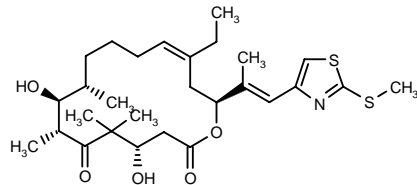


C27 H41 N O5 S2; Mol wt: 523.7549

ACTION – Antineoplastic agent that acts as an enhancer of microtubule polymerization, as demonstrated using pig brain microtubule protein (78% polymerization relative to epothilone B = 100%), proven to inhibit the growth of human epidermoid cancer KB-31 cells (IC₅₀ = 4.03 nM). Other exemplified compounds from this series of 13-alkyl epothilone derivatives include the following:



304317: C28 H43 N O5 S2



304318: C28 H43 N O5 S2

SOURCES – Novartis; Scripps Research Institute, La Jolla, CA (US).

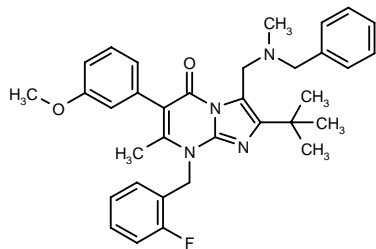
REFERENCES

1. Sinha, S.C. et al. (Novartis AG; Scripps Research Institute) *13-Alkyl epothilone derivs*. WO 0127308.

HORMONAL AGENTS

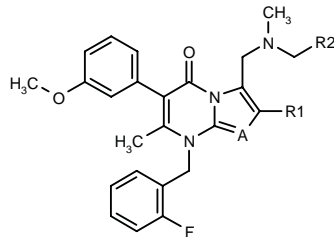
304113

3-(*N*-Benzyl-*N*-methylaminomethyl)-2-*tert*-butyl-8-(2-fluorobenzyl)-6-(3-methoxyphenyl)-7-methylimidazo-[1,2-*a*]pyrimidin-5(8*H*)-one

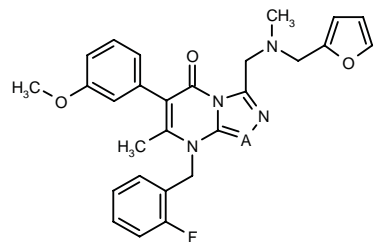


C34 H37 F N4 O2; Mol wt: 552.6903

ACTION – Gonadotropin-releasing hormone (GnRH) receptor antagonist that is expected to be useful for the treatment of sex hormone-related disorders including prostatic, uterine and breast cancers, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids or precocious puberty. Other specifically claimed compounds include the following:



Compound	R1	R2	A	Formula
304114	t-Bu	2-Pyr	N	C ₃₃ H ₃₆ FN ₅ O ₂
304115	CH ₂ CO ₂ Et	2-Pyr-CH ₂	N	C ₃₄ H ₃₆ FN ₅ O ₄
304116	t-Bu	2-Pyr-CH ₂	CH	C ₃₅ H ₃₉ FN ₄ O ₂



Compound	A	Formula
304117	CH	C ₂₈ H ₂₇ FN ₄ O ₃
304118	N	C ₂₇ H ₂₆ FN ₅ O ₃

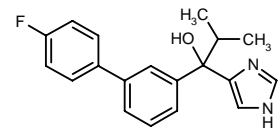
SOURCE – Neurocrine Biosciences.

REFERENCES

1. Zhu, Y.-F. et al. (Neurocrine Biosciences Inc.) *Gonadotropin-releasing hormone receptor antagonists and methods relating thereto*. WO 0129044.

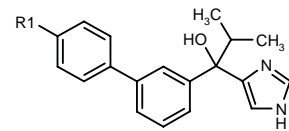
304443

1-(4'-Fluorobiphenyl-3-yl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol



C19 H19 F N2 O; Mol wt: 310.3701

ACTION – Steroid C_{17,20} lyase (steroid 17- α -monooxygenase) inhibitor (IC₅₀ = 8.3 nM in rat testicular microsomes) found to inhibit testosterone biosynthesis in rats at a dose of 50 mg/kg p.o. Potentially useful for the treatment of prostate cancer, breast cancer, prostatic hypertrophy, hirsutism, male pattern baldness, uterine myoma, endometriosis and polycystic ovary syndrome. Other exemplified compounds from this series of 1-substituted phenyl-1-(1*H*-imidazol-4-yl) alcohols include the following:



Compound	R1	Formula
304444	H	C ₁₉ H ₂₀ N ₂ O
304445	OMe	C ₂₀ H ₂₂ N ₂ O ₂

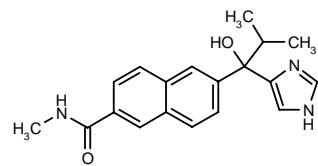
SOURCE – Takeda.

REFERENCES

1. Tasaka, A. et al. (Takeda Chemical Industries, Ltd.) *1-Substd. phenyl-1-(1H-imidazol-4-yl) alcohols, process for producing the same and use thereof*. JP 2001187784, WO 0130764.

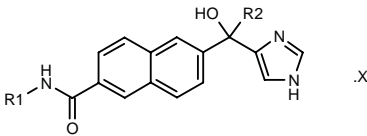
304600

6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methylnaphthalen-2-carboxamide



C19 H21 N3 O2; Mol wt: 323.3939

ACTION – Steroid C_{17,20} lyase (steroid 17- α -monooxygenase) inhibitor (IC₅₀ = 6.2 nM in rat testicular microsomes) proven to inhibit testosterone biosynthesis in rats at 50 mg/kg p.o. with a T/C value of 4.5%. This compound is expected to be useful for the treatment of prostate cancer, breast cancer, prostatic hypertrophy, hirsutism, male pattern baldness, uterine myoma, endometriosis and polycystic ovary syndrome. Other exemplified imidazol-4-ylmethanols are:



Compound	R1	R2	Isomer	X	Formula
304601	i-Pr	i-Pr			C ₂₁ H ₂₅ N ₃ O ₂
304602	cyclopropyl	i-Pr			C ₂₁ H ₂₃ N ₃ O ₂
304604	Me	Et			C ₁₈ H ₁₉ N ₃ O ₂
304605	Me	i-Bu			C ₂₀ H ₂₃ N ₃ O ₂
304606	Me	i-Pr	S		C ₁₉ H ₂₁ N ₃ O ₂
304607	cyclopropyl	i-Pr	S		C ₂₁ H ₂₃ N ₃ O ₂
304608	i-Pr	i-Pr	S		C ₂₁ H ₂₅ N ₃ O ₂
304609	Me	Et	S		C ₁₈ H ₁₉ N ₃ O ₂
304610	Me	Et	S	fumarate	C ₁₈ H ₁₉ N ₃ O ₂ ·C ₄ H ₄ O ₄

SOURCE – Takeda.

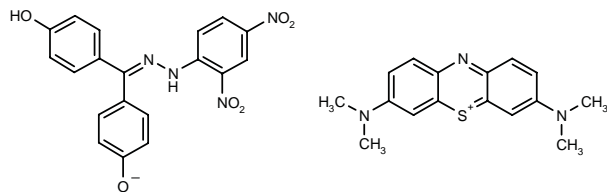
REFERENCES

1. Tasaka, A. et al. (Takeda Chemical Industries, Ltd.) *Imidazol-4-ylmethanols use as inhibitors of steroid C17-20 lyase*. WO 0130762.

A-007/MEB

306966

3,7-Bis(dimethylamino)phenothiazin-5-ium 4-[(2,4-dinitrophenylhydrazono)(4-hydroxyphenyl)methyl]phenolate



C35 H31 N7 O6 S ; Mol wt: 677.7389

ACTION – Stable double salt of methylene blue and the antiestrogen A-007⁺, with improved *in vitro* cytotoxic activity and percutaneous absorption in rat skin. Potentially useful for the treatment of malignant cutaneous metastases.

SOURCE – Dekk-Tek.

REFERENCES

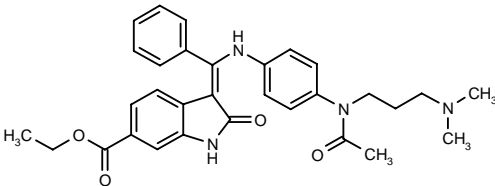
1. Morgan, L.R. et al. *Anticancer properties for 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone (A-007)/3,7-diaminophenothiazin-5-ium double salts*. Bioorg Med Chem Lett 2001, 11(16): 2193.

*Drug Data Rep 1990, 012(10): 0831.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

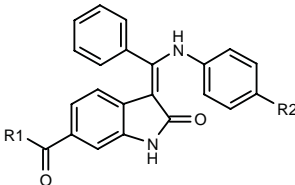
303945

(Z)-3-[1-[4-[N-Acetyl-N-[3-(dimethylamino)propyl]-amino]phenylamino]-1-phenylmethylene]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylic acid ethyl ester



C31 H34 N4 O4 ; Mol wt: 526.6336

ACTION – An inhibitor of different receptor tyrosine kinases and cyclin/CDK complexes, shown to inhibit the proliferation of endothelial and tumor cells; *in vitro*, compound inhibited the proliferation of human umbilical vein endothelial cells (HUVEC) stimulated with VEGF (vascular endothelial growth factor)–heparin with an IC₅₀ value of 0.003 μM. Other exemplified compounds from this series of 6-substituted indoline derivatives include the following:



Compound	R1	R2	Formula
303946	OEt	1-Pip-CH2	C ₃₀ H ₃₁ N ₃ O ₃
303947	NH2	1-Pip-CH2	C ₂₈ H ₂₈ N ₄ O ₂
303948	OMe	1-Pip-CH2	C ₂₉ H ₂₉ N ₃ O ₃
303949	OEt	CH2N(Me)2	C ₂₇ H ₂₇ N ₃ O ₃
303950	OEt	2,6-(Me)2-1-Pip-CH2	C ₃₂ H ₃₆ N ₃ O ₃
303951	OEt	N(Ac)CH2CH2N(Me)2	C ₃₀ H ₃₂ N ₄ O ₄
303952	OEt	N(SO2Me)CH2CH2N(Me)2	C ₂₉ H ₃₂ N ₄ O ₅ S
303953	OMe	CH2N(Me)2	C ₂₆ H ₂₆ N ₃ O ₃
303954	OMe	N(Ac)CH2CON(Me)2	C ₂₉ H ₂₈ N ₄ O ₅
303955	OMe	CH2NHEt	C ₂₆ H ₂₆ N ₃ O ₃
303957	OMe	1-Me-2-imidazolyl	C ₂₇ H ₂₂ N ₄ O ₃
303958	OMe	N(Me)COCH2N(Me)2	C ₂₈ H ₂₈ N ₄ O ₄
303959	OMe	N(SO2Me)CH2CH2N(Me)2	C ₂₈ H ₃₀ N ₄ O ₅ S
303960	OMe	N(SO2Me)(CH2)3N(Me)2	C ₂₉ H ₃₂ N ₄ O ₅ S
303962	OMe	N(SO2Me)CH2CON(Me)2	C ₂₈ H ₂₈ N ₄ O ₆ S
303964	OMe	N(Me)COCH2CH2N(Me)2	C ₂₉ H ₃₀ N ₄ O ₄
303965	OMe	N(Ac)CH2CH2N(Me)2	C ₂₉ H ₃₀ N ₄ O ₄
303966	OMe	CH2NHMe	C ₂₅ H ₂₃ N ₃ O ₃

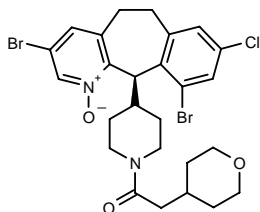
SOURCE – Boehringer Ingelheim.

REFERENCES

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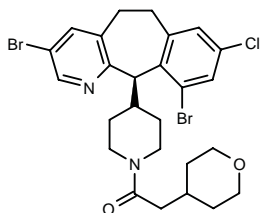
304350

3,10-Dibromo-8-chloro-11(*R*)-[1-[2-(tetrahydropyran-4-yl)-acetyl]piperidin-4-yl]-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine 1-oxide



C26 H29 Br2 Cl N2 O3; Mol wt: 612.7871

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC_{50} = 2.2 nM) proven to inhibit Ras processing in COS cells (100% inhibition at 10 nM). Compound was also shown to inhibit anchorage-independent growth of human tumor cell lines in a soft agar assay with an IC_{50} value of 8 nM. Another specifically claimed tricyclic compound is:



304351: C26 H29 Br2 Cl N2 O2

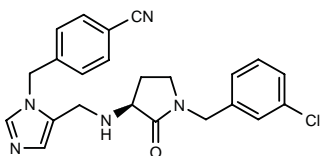
SOURCE – Schering-Plough.

REFERENCES

1. Doll, R.J. et al. (Schering Corp.) *Cpds. useful for inhibition of farnesyl protein transferase*. US 6228865.

306506

4-[5-[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3(*S*)-ylamino-methyl]-1*H*-imidazol-1-ylmethyl]benzonitrile



C23 H22 Cl N5 O; Mol wt: 419.9138

ACTION – Nonpeptide protein farnesyltransferase inhibitor (IC_{50} = 1.9 and 0.52 nM against purified enzyme and in a cell-based assay, respectively) with high selectivity over protein geranylgeranyltransferase (IC_{50} = 3400 nM). Compound inhibited the anchorage-independent growth of H-*ras* transformed Rat1 cells (IC_{50} = 4.1 nM), as well as of a variety of transformed human tumor cells such as human lung carcinoma A549, colon adenocarcinoma COLO 205, colon cancer LS180 and human epidermoid cancer KB-31 cells (IC_{50} = 320-530 nM). In an *in vivo* model of cancer, using K-*rasB* transgenic mice, compound at doses of 120 and 40 mg/kg/day by s.c. infusion produced regression of primary tumor and decreased total tumor volume. In dogs it showed an

excellent oral bioavailability and low plasma clearance, but its relatively short plasma half-life and proarrhythmic activity make it unsuitable for oral dosing.

SOURCE – Merck & Co.

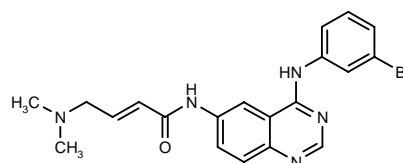
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306769

N-[4-(3-Bromophenylamino)quinazolin-6-yl]-4-(dimethylamino)-2(*E*)-butenamide



C20 H20 Br N5 O; Mol wt: 426.3160

ACTION – Antineoplastic agent, an irreversible inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2) tyrosine kinases (IC_{50} = 0.011 and 0.301 μ M, respectively) found to strongly inhibit the growth of several human cancer cell lines including epidermoid carcinoma A-431, breast cancer SK-BR-3 and colon cancer SW620 cells (IC_{50} = 94, 2 and 2336 nM, respectively). *In vivo* in mice bearing A-431 xenografts, compound given orally at 40 mg/kg/day for 10 days strongly inhibited (> 90%) tumor growth even 12 days after stopping treatment.

SOURCE – American Home Products.

REFERENCES

1. Wissner, A. et al. (American Cyanamid Co.) *Substd. quinazoline derivs. and their use as tyrosine kinase inhibitors*. EP 1000039, WO 9909016.

2. Tsou, H.-R. et al. *6-Substituted-4-(3-bromophenylamino)quinazolines as putative irreversible inhibitors of the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2) tyrosine kinases with enhanced antitumor activity*. J Med Chem 2001, 44(17): 2719.

EMD-72000

306297

Humanized IgG₁ anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody

ACTION – Antineoplastic agent, a humanized monoclonal antibody against epidermal growth factor receptor (EGFR) proven to significantly reduce the size of EGFR-overexpressing squamous cell carcinoma A-431 and Detroit 562 xenografts in mice. A phase I clinical trial in patients with stage III and IV squamous cell carcinoma of the head and neck showed a favorable toxicity profile for compound; the proposed dose for long-term studies is 200 mg i.v. weekly without a loading dose. Potentially useful as adjuvant therapy for cancers that express the EGFR including head and neck cancer.

SOURCE – Merck KGaA.

REFERENCES

1. Bier, H. et al. *Anti-(epidermal growth factor) receptor monoclonal antibodies for the induction of antibody-dependent cell-mediated cytotoxicity against squamous cell carcinoma lines of the head and neck*. Cancer Immunol Immunother 1998, 46(3): 167.

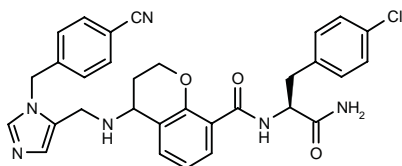
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3. Hambek, M. et al. *Tumor necrosis factor α sensitizes low epidermal growth factor receptor (EGFR)-expressing carcinomas for anti-EGFR therapy*. Cancer Res 2001, 61(3): 1045.

RPR-201764

307199

4-Chloro-*N*-[4-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl-methylamino]-1-benzopyran-8-ylcarbonyl]-*L*-phenylalaninamide



C31 H29 Cl N6 O3; Mol wt: 569.0621

ACTION – Potent and orally available protein farnesyl-transferase inhibitor (IC_{50} = 2 nM), potentially useful as an antineoplastic agent.

SOURCE – Aventis Pharma.

REFERENCES

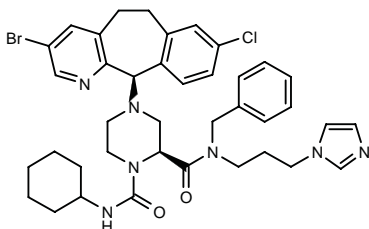
1. Baudoin, B. et al. (Aventis Pharma SA) *Condensed heterocyclic system derivs., preparation, pharmaceutical compsns. containing them*. EP 1054882, FR 2774987, WO 9941248.

2. Jimonet, P. et al. *High throughput organic synthesis, crystallography and early ADME integration applied to the discovery of potent and orally bioavailable chromane and benzoxazine farnesyltransferase inhibitors*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 3.

SCH-222422

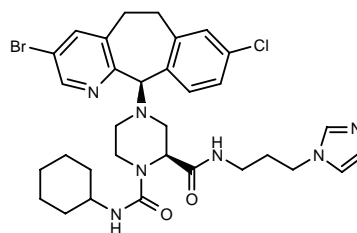
307201

*N*²-Benzyl-4-[3-bromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]-*N*¹-cyclohexyl-*N*²-[3-(1*H*-imidazol-1-yl)propyl]piperidine-1,2(*S*)-dicarboxamide

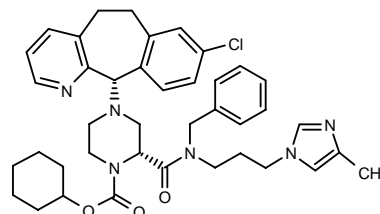


C39 H45 Br Cl N7 O2; Mol wt: 759.1885

ACTION – Antineoplastic agent, an orally available protein farnesyltransferase inhibitor (IC_{50} = 0.26 nM) proven to inhibit the growth of human cancer cells *in vitro*. Other next-generation inhibitors are:



SCH-211618[274358]*: C32 H39 Br Cl N7 O2



SCH-226374[291869]**: C40 H47 Cl N6 O3

SOURCES – Pharmacopeia; Schering-Plough.

REFERENCES

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3. Taveras, A.G. et al. *Sch-66636 and beyond: Discovering next-generation inhibitors of farnesyl protein transferase*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 4.

*Identified compound **274358** (see **274338**) Drug Data Rep 1999, 021(04): 0365.

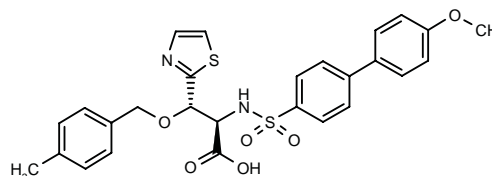
Identified compound **291869 Drug Data Rep 2000, 022(11): 1029.

ANGIOGENESIS INHIBITORS

303802

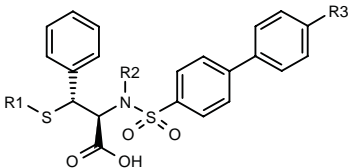
N-(4'-Methoxybiphenyl-4-ylsulfonyl)-3-*O*-(4-methylbenzyl)-3(*S*)-(2-thiazolyl)-*D*-serine

2(*R*)-(4'-Methoxybiphenyl-4-ylsulfonamido)-3(*S*)-(4-methylbenzyl)-3-(2-thiazolyl)propionic acid

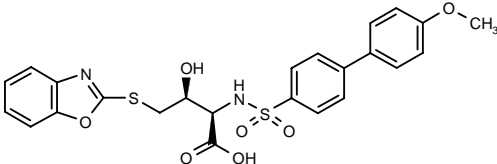


C27 H26 N2 O6 S2; Mol wt: 538.6424

ACTION – Matrix metalloproteinase inhibitor, claimed for the treatment of arthritis, cancer, cardiovascular disorders, skin disorders, ocular disorders, inflammation and gum disease. Other exemplified compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	R3	Formula
303806	Et	H	F	C ₂₃ H ₂₂ FNO ₄ S ₂
303809	Ph	H	OMe	C ₂₆ H ₂₅ NO ₅ S ₂
303811	2-pyrimidinyl	H	Br	C ₂₅ H ₂₀ BrN ₃ O ₄ S ₂
303813	2-oxazolyl	H	Cl	C ₂₄ H ₁₉ ClN ₂ O ₅ S ₂
303815	Ph	CH ₂ Ph	OMe	C ₃₅ H ₃₁ NO ₅ S ₂
303816	1-Me-2-imidazolyl	H	OMe	C ₂₆ H ₂₅ N ₃ O ₅ S ₂
303817	1-Me-1,2,4-triazol-3-yl	H	SMe	C ₂₅ H ₂₄ N ₄ O ₄ S ₃
303818	CH ₂ CH ₂ OPh	H	OMe	C ₃₀ H ₂₉ NO ₆ S ₂
303821	2-benzothiazolyl	H	OMe	C ₂₉ H ₂₄ N ₂ O ₅ S ₃



303820: C24 H22 N2 O7 S2

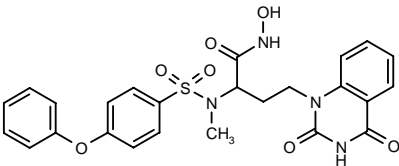
SOURCE – Procter & Gamble.

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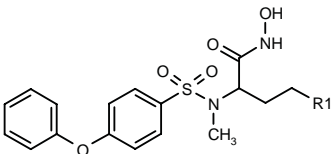
304001

4-(2,4-Dioxo-1,2,3,4-tetrahydroquinazolin-1-yl)-2-[N-methyl-N-(4-phenoxyphenylsulfonyl)amino]butyrohydroxamic acid



C25 H24 N4 O7 S; Mol wt: 524.5516

ACTION – Matrix metalloproteinase (MMP) inhibitor active against MMP-13 (collagenase 3) and aggrecanase, potentially useful for the treatment of arthritis and cancer. *In vitro*, compound inhibited MMP-13 from human chondrosarcoma HCS-2/8 cells with an IC₅₀ of 0.36 nM. Other exemplified sulfonamide derivatives include the following:



Compound	R1	Formula
304005	2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-1-yl	C ₂₄ H ₂₃ N ₅ O ₇ S
304007	6-Me-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl	C ₂₂ H ₂₄ N ₄ O ₇ S

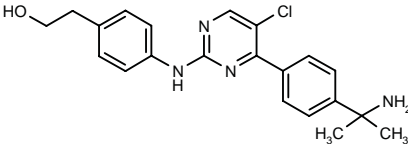
SOURCE – Sankyo.

REFERENCES

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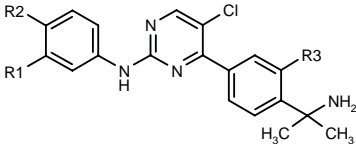
304206

2-[4-[4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloropyrimidin-2-ylamino]phenyl]ethanol



C21 H23 Cl N4 O; Mol wt: 382.8927

ACTION – Selective KDR kinase and/or fibroblast growth factor (FGF) receptor kinase inhibitor, potentially useful for the treatment or prevention of disease states associated with angiogenesis such as cancer, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, ischemic heart disease, atherosclerosis and ocular diseases such as diabetic retinopathy. Other specifically claimed compounds from this series of 4,5-disubstituted-2-aminopyrimidines are:



Compound	R1	R2	R3	Formula
304207	CH ₂ CH ₂ OH	H	H	C ₂₁ H ₂₃ ClN ₄ O
304208	H	1-imidazolyl	H	C ₂₂ H ₂₁ ClN ₆
304209	H	CH ₂ CH ₂ OH	F	C ₂₁ H ₂₂ ClFN ₄ O
304210	H	1-imidazolyl-CH ₂ CH ₂	H	C ₂₄ H ₂₅ ClN ₆
304211	H	2-Me-1-imidazolyl-CH ₂ CH ₂	H	C ₂₆ H ₂₇ ClN ₆
304212	H	2-i-Pr-1-imidazolyl-CH ₂ CH ₂	H	C ₂₇ H ₃₁ ClN ₆
304213	H	4-thiomorpholinyl-CH ₂ CH ₂	H	C ₂₅ H ₃₀ ClN ₅ S
304214	H	t-BuNHCH ₂ CH ₂	H	C ₂₅ H ₃₂ ClN ₅
304215	H	4-Me-1-Piz-CH ₂ CH ₂	H	C ₂₆ H ₃₃ ClN ₆
304216	H	4-Et-1-Piz-CH ₂ CH ₂	H	C ₂₇ H ₃₅ ClN ₆
304217	H	3,5-(Me)2-1-Piz-CH ₂ CH ₂	H	C ₂₇ H ₃₅ ClN ₆
304218	H	4-(2-Pyr)-1-Piz-CH ₂ CH ₂	H	C ₃₀ H ₃₄ ClN ₇
304219	H	1-pyrrolidinyl-CH ₂ CH ₂	H	C ₂₅ H ₃₀ ClN ₅
304220	H	1-Pip-CH ₂ CH ₂	H	C ₂₆ H ₃₂ ClN ₅

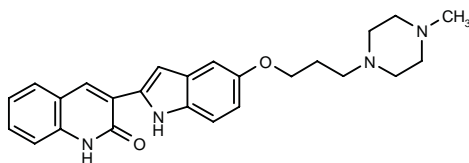
SOURCE – Celltech Group.

REFERENCES

1. Davis, J.M. and Moffat, D.F.C. (Celltech Chiroscience Ltd.) *4,5-Disubstd.-2-aminopyrimidines*. WO 0129009.

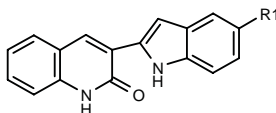
304229

3-[5-[3-(4-Methylpiperazin-1-yl)propoxy]-1*H*-indol-2-yl]-quinolin-2(1*H*)-one



C₂₅ H₂₈ N₄ O₂; Mol wt: 416.5222

ACTION – Angiogenesis inhibitor that acts by inhibiting tyrosine kinase enzymes, particularly vascular endothelial growth factor (VEGF) receptor kinase. The compound is expected to be useful for the treatment of cancer, retinal vascularization, diabetic retinopathy, age-related macular degeneration, inflammatory diseases including rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity, and bone-associated disorders including osteosarcoma, osteoarthritis and rickets. Other specifically claimed compounds from this series of indole derivatives include the following:



Compound	R1	Formula
304230	4(R)-MeO-2(S)-pyrrolidinyl-CH ₂ O	C ₂₃ H ₂₃ N ₃ O ₃
304231	4-CO ₂ H-1-Pip-CH ₂ CH ₂ O	C ₂₅ H ₂₅ N ₃ O ₄
304232	4-Ac-1-Piz-CH ₂	C ₂₄ H ₂₄ N ₄ O ₂
304233	4-Me-1-Piz-CO	C ₂₃ H ₂₂ N ₄ O ₂
304234	4-(NH ₂ CO)-1-Pip-CH ₂	C ₂₄ H ₂₄ N ₄ O ₂
304235	4-Ac-1-Piz-CH(Me)	C ₂₅ H ₂₆ N ₄ O ₂
304236	4-NH ₂ -1-Pip-CONHCH ₂	C ₂₄ H ₂₅ N ₅ O ₂

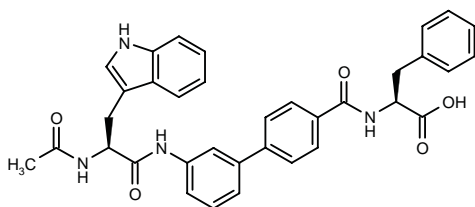
SOURCE – Merck & Co.

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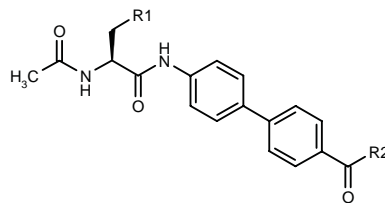
304453

N-[3'-(*N*-Acetyl-L-tryptophylamino)biphenyl-4-ylcarbonyl]-L-phenylalanine

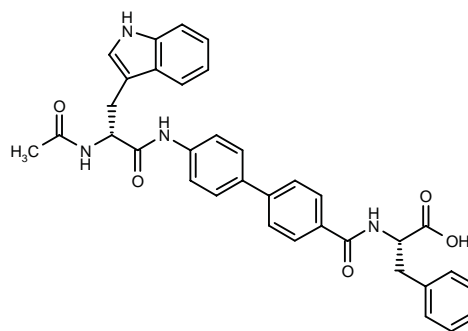


C₃₅ H₃₂ N₄ O₅; Mol wt: 588.6608

ACTION – Antineoplastic, antimetastatic, antiangiogenic and antiinflammatory agent, an inhibitor of urokinase-type plasminogen activator (uPA) binding to uPA receptors (uPAR; IC₅₀ = 0.8 nM). Other compounds from this series of aminobenzoic and aminobiphenylcarboxylic acids include the following:



Compound	R1	R2	Formula
304454	3-indolyl	-β-Ala-OH	C ₂₉ H ₂₈ N ₄ O ₅
304455	3-indolyl	-L-Phe-OH	C ₃₅ H ₃₂ N ₄ O ₅
304457	3-indolyl	-D-Phe-OH	C ₃₅ H ₃₂ N ₄ O ₅
304458	CH ₂ CONH ₂	-L-Phe-OH	C ₂₉ H ₃₀ N ₄ O ₆
304459	3-indolyl	-L-Tyr-OH	C ₃₅ H ₃₂ N ₄ O ₆
304460	3-indolyl	-L-Asp-NH ₂	C ₃₀ H ₂₉ N ₅ O ₆



304456: C₃₅ H₃₂ N₄ O₅

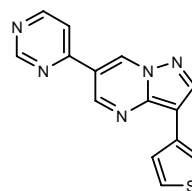
SOURCE – Schering-Plough.

REFERENCES

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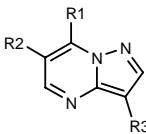
304672

6-(4-Pyrimidinyl)-3-(3-thienyl)pyrazolo[1,5-*a*]pyrimidine



C₁₄ H₉ N₅ S; Mol wt: 279.3261

ACTION – Agent for the treatment of cancer and ocular disorders such as diabetic retinopathy, an inhibitor of vascular endothelial growth factor (VEGF) receptor kinase reported to show selectivity over related tyrosine kinases such as FGFR1 and Src family kinases. Other specifically claimed compounds from this series of pyrazolo[1,5-*a*]pyrimidine derivatives are:



Compound	R1	R2	R3	Formula
304673	H	4-Me-Ph	3-thienyl	C ₁₇ H ₁₃ N ₃ S
304675	H	4-MeO-Ph	3-thienyl	C ₁₇ H ₁₃ N ₃ OS
304676	H	4-MeO-Ph	4-Pyr	C ₁₈ H ₁₄ N ₄ O
304677	H	4-Cl-Ph	4-Pyr	C ₁₇ H ₁₁ ClN ₄
304678	H	4-Me-Ph	4-Pyr	C ₁₈ H ₁₄ N ₄
304679	H	2-Pyr	4-Pyr	C ₁₆ H ₁₁ N ₅
304680	H	4-pyrimidinyl	4-Pyr	C ₁₅ H ₁₀ N ₆
304681	H	2-pyrazinyl	4-Pyr	C ₁₅ H ₁₀ N ₆
304682	H	4-MeO-Ph	3-Pyr	C ₁₈ H ₁₄ N ₄ O
304683	H	4-Pyr	3-Pyr	C ₁₆ H ₁₁ N ₅
304684	H	4-OH-Ph	3-thienyl	C ₁₆ H ₁₁ N ₃ OS
304685	H	cyclohexyl	3-thienyl	C ₁₆ H ₁₇ N ₃ S
304686	H	4-Pyr	3-thienyl	C ₁₅ H ₁₀ N ₄ S
304687	4-Pyr	H	3-thienyl	C ₁₅ H ₁₀ N ₄ S

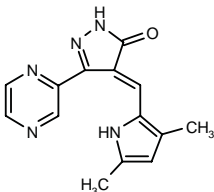
SOURCE – Merck & Co.

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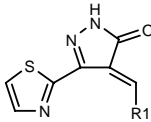
304713

4-(3,5-Dimethyl-1*H*-pyrrol-2-ylmethylene)-5-(2-pyrazinyl)-3,4-dihydro-2*H*-pyrazol-3-one



C14 H13 N5 O; Mol wt: 267.2907

ACTION – An inhibitor of kinases such as vascular endothelial growth factor (VEGF) receptor kinase, trkA tyrosine kinase, mixed-lineage kinase (MLK) and fibroblast growth factor (FGF) receptor kinase, as demonstrated *in vitro* by 74, 88, 53, 44, 17, 72 and 48% inhibition, respectively, of VEGFR1, VEGFR2, trkA, MLK-1, MLK-2, MLK-3 and FGFR1 kinase activity at a concentration of 1 μM. Potentially useful for the treatment or prevention of angiogenic disorders, particularly cancer, endometriosis, diabetic retinopathy, psoriasis and macular degeneration, as well as CNS disorders such as Alzheimer’s disease, amyotrophic lateral sclerosis, Parkinson’s disease, stroke, Huntington’s disease, epilepsy, multiple sclerosis, and osteoporosis, inflammation, transplant rejection and viral infections. Other exemplified compounds from this series of heterocyclic substituted pyrazolones include the following:



Compound	R1	Formula
304714	3-indolyl	C ₁₅ H ₁₀ N ₄ OS
304715	3,5-(Me)2-2-pyrrolyl	C ₁₃ H ₁₂ N ₄ OS
304716	1-Me-3-indolyl	C ₁₆ H ₁₂ N ₄ OS

SOURCE – Cephalon.

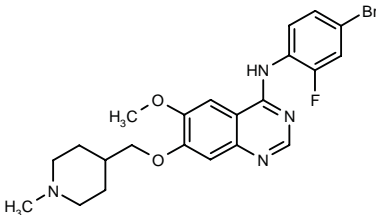
REFERENCES

1. Singh, J. and Tripathy, R. (Cephalon, Inc.) *Heterocyclic substd. pyrazolones*. WO 0132653.

ZD-6474

304792

N-(4-Bromo-2-fluorophenyl)-6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)quinazolin-4-amine



C22 H24 Br F N4 O2; Mol wt: 475.3596

ACTION – Orally active vascular endothelial growth factor (VEGF) receptor (KDR) tyrosine kinase inhibitor (IC₅₀ = 40 nM) able to inhibit VEGF-induced endothelial cell proliferation *in vitro* (IC₅₀ = 60 nM). Compound (12.5-100 mg/kg/day p.o.) exhibited broad-spectrum activity against a panel of human tumor xenografts in mice including prostate, lung, breast, ovarian, vulvar and colon tumors. The antitumor activity of the compound was consistent with its antiangiogenic activity; chronic administration of compound induced hypertrophy of the femorotibial epiphyseal growth plate due to inhibition of VEGF-induced angiogenesis. Preliminary results of a phase I study in patients with solid tumors showed that compound given at 50 and 100 mg produced dose-related plasma levels and minimal toxicity.

SOURCE – AstraZeneca.

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6. Wedge, S.R. et al. *Dynamic contrast-enhanced MRI study of human tumor xenografts treated with the VEGF signaling inhibitor ZD6474*. Proc Amer Assoc Cancer Res 2001, 42: Abst 581.

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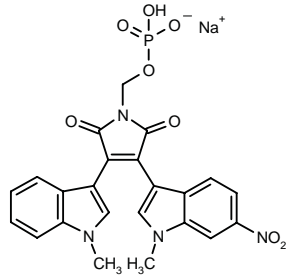
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12. *AstraZeneca takes an ambitious approach to drug R&D*. DailyDrugNews.com (Daily Essentials) 1999, , Dec 13.

OTHER ONCOLYTIC DRUGS

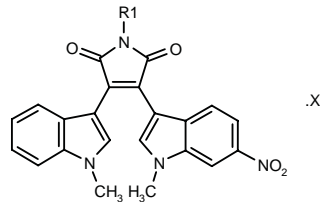
303771

Phosphoric acid 3-(1-methyl-1*H*-indol-3-yl)-4-(1-methyl-6-nitro-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-ylmethyl ester sodium salt



C23 H18 N4 Na O8 P; Mol wt: 532.3792

ACTION – Antineoplastic agent proven to inhibit the proliferation of human mammary carcinoma MDA-MB-435 cells with an IC₅₀ value of 1.00 μM or less. Compound is suitable for administration as a continuous infusion. Other specifically claimed compounds from this series of substituted pyrroles are:



Compound	R1	X	Formula
303772	CONH(CH2)4OPO(OH)O ⁻	Na ⁺	C ₂₇ H ₂₅ N ₅ NaO ₉ P
303773	CH2OCOCH2CH2(OCH2CH2) <i>n</i> OMe		C ₂₇ H ₂₄ N ₄ O ₇ (C ₂ H ₄ O) <i>n</i>
303774	CH2OCOCH2(OCH2CH2) <i>n</i> OMe		C ₂₆ H ₂₂ N ₄ O ₇ (C ₂ H ₄ O) <i>n</i>
303970	1-Me-3-Pyr-COOCH2	CF3CO2 ⁻	C ₃₂ H ₂₄ F ₃ N ₅ O ₈

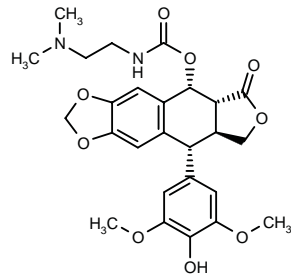
SOURCE – Roche.

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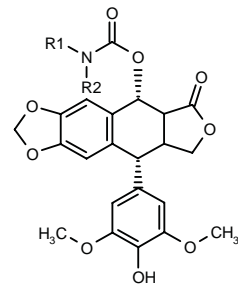
304268

N-[2-(Dimethylamino)ethyl]carbamic acid (5*R*,5*aR*,8*aS*,9*R*)-9-(4-hydroxy-3,5-dimethoxyphenyl)-6-oxo-5,5*a*,6,8,8*a*,9-hexahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-5-yl ester



C26 H30 N2 O9; Mol wt: 514.5280

ACTION – Antitumor agent with excellent cytotoxic activity, as demonstrated *in vitro* against murine leukemia L1210 and human colon carcinoma HT-29 cells (IC₅₀ = 88 nM). This compound induced a 75% accumulation of L1210 cells in the G2/M phase after 21 h of incubation at 1 μM. Other specifically claimed podophyllotoxin derivatives are:



Compound	R1	R2	Isomer	Formula
304269	H	4-F-Ph	5 <i>aR</i> ,8 <i>aS</i>	C ₂₈ H ₂₄ FNO ₉
304270	Me	CH2CH2N(Me)2	5 <i>aS</i> ,8 <i>aR</i>	C ₂₇ H ₃₂ N ₂ O ₉
304272	Me	(CH2)3N(Me)2	5 <i>aR</i> ,8 <i>aS</i>	C ₂₈ H ₃₄ N ₂ O ₉
304275	H	(CH2)3N(Me)2	5 <i>aS</i> ,8 <i>aR</i>	C ₂₇ H ₃₂ N ₂ O ₉

SOURCE – ADIR.

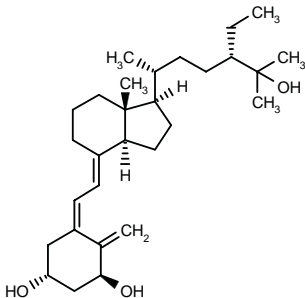
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304354

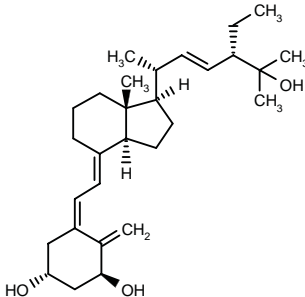
(1*S*,3*R*,5*Z*,7*E*,24*S*)-9,10-Secostigmasta-5,7,10-triene-1,3,25-triol

24(*S*)-Ethyl-1α,25-dihydroxyvitamin D₃



C29 H48 O3; Mol wt: 444.6952

ACTION – Agent for the treatment of hyperproliferative diseases, osteoporosis and immunological disorders with a relative binding affinity (1,25-dihydroxyvitamin D₃ = 1.0) for the 1,25-dihydroxyvitamin D₃ receptor (VDR) of 0.01, reported to possess little calcemic activity. Compound was shown to induce the differentiation of human myelogenous leukemia HL-60 cells, although with lower potency than 1,25-dihydroxyvitamin D₃ (66 and 44%, respectively, at 0.1 and 0.01 μM vs. 77 and 65% for 1,25-dihydroxyvitamin D₃ at the same concentrations). Another compound from this series of vitamin D derivatives is:



304356: C29 H46 O3

SOURCE – Nisshin Flour Milling.

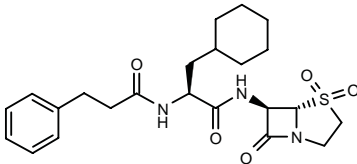
REFERENCES

1. Tachibana, Y. (Nisshin Flour Milling Co., Ltd.) *Active vitamin D derivs.* JP 2001089442.

304416

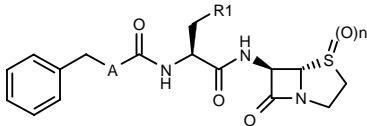
N-(3-Phenylpropionyl)-3-cyclohexyl-L-alanine [(5*S*,6*R*)-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl]amide

3-Cyclohexyl-2(*S*)-(3-phenylpropionamido)-*N*-[(5*S*,6*R*)-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl]propionamide

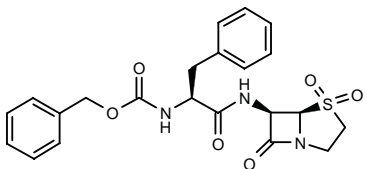


C23 H31 N3 O5 S; Mol wt: 461.5799

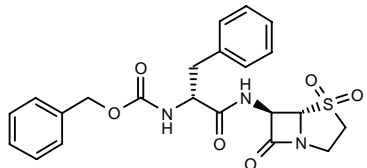
ACTION – An inhibitor of cysteine proteases such as cathepsin B and cathepsin L (IC₅₀ = 0.43 and 0.0007 μM, respectively, against rat enzymes), potentially useful for the treatment or a broad range of disorders including cancer, osteoporosis, rheumatoid arthritis, muscular dystrophy, myocardial infarction, pulmonary emphysema, septic shock, cerebral ischemia, impaired memory function, Alzheimer’s disease, cataracts, malaria, inflammatory diseases and bacterial, parasitic and viral infections. Other specifically claimed compounds from this series of substituted amino bicyclic β-lactam penam and cepham derivatives are:



Compound	R1	A	n	Formula
304419	Ph	O	0	C ₂₂ H ₂₃ N ₃ O ₄ S
304420	Ph	O	2	C ₂₂ H ₂₃ N ₃ O ₆ S
304422	cyclohexyl	CH2	0	C ₂₃ H ₃₁ N ₃ O ₃ S
304423	2-Naph	CH2	0	C ₂₇ H ₂₇ N ₃ O ₃ S
304424	2-Naph	CH2	2	C ₂₇ H ₂₇ N ₃ O ₅ S
304425	2-thienyl	CH2	0	C ₂₁ H ₂₃ N ₃ O ₃ S ₂
304426	2-thienyl	CH2	2	C ₂₁ H ₂₃ N ₃ O ₅ S ₂
304427	3-F-Ph	CH2	0	C ₂₃ H ₂₄ FN ₃ O ₃ S
304428	3-F-Ph	CH2	2	C ₂₃ H ₂₄ FN ₃ O ₅ S
304429	3-Pyr	O	0	C ₂₁ H ₂₂ N ₄ O ₄ S
304430	3-Pyr	O	2	C ₂₁ H ₂₂ N ₄ O ₆ S
304432	Ph	O	1	C ₂₂ H ₂₃ N ₃ O ₅ S



304421: C22 H23 N3 O6 S



304431: C22 H23 N3 O6 S

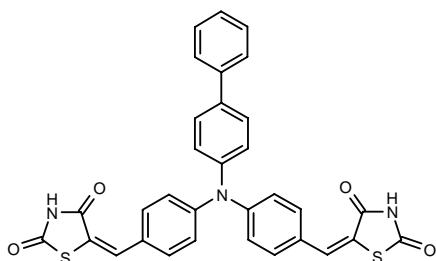
SOURCE – Naeja Pharmaceuticals.

REFERENCES

1. Singh, R. et al. (Naeja Pharmaceuticals Inc.) *Substd. amino bicyclic-β-lactam penam and cepham derivs. as cysteine protease inhibitors.* US 6232305.

304500

5,5'-(4-Biphenylimino)bis(1,4-phenylene)bis(methylidene)bis(thiazolidine-2,4-dione)



C32 H21 N3 O4 S2; Mol wt: 575.6669

ACTION – Antineoplastic agent with telomerase-inhibitory activity, as demonstrated *in vitro* in assays using nuclear extracts from HEK-293 cells (IC_{50} = 50 μ M or less) and human renal cancer ACHN cells (at least 50% inhibition at 30 μ M). A representative compound from a series of thiazolidinedione derivatives.

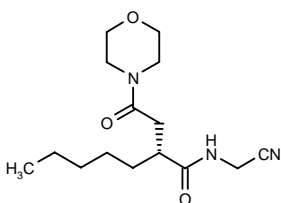
SOURCE – Kyowa Hakko.

REFERENCES

1. Akama, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Thiazolidinedione derivs.* WO 0130771.

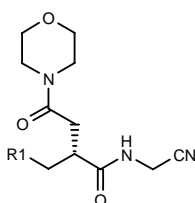
304513

N-(Cyanomethyl)-2(*R*)-[2-(4-morpholinyl)-2-oxoethyl]-heptanamide



C15 H25 N3 O3; Mol wt: 295.3805

ACTION – An inhibitor of cysteine proteases, particularly cathepsin L and/or cathepsin S, potentially useful for the treatment of diseases mediated by cysteine proteases such as autoimmune and inflammatory diseases, tumor metastasis, tissue damage following myocardial infarction, bone resorption, muscular dystrophy and chronic obstructive pulmonary disease (COPD). Other exemplified compounds from this series of acylated aminoacetanitriles are:



Compound	R1	Formula
304514	CH ₂ CH ₂ Ph	C ₁₉ H ₂₆ N ₃ O ₃
304515	i-Pr	C ₁₄ H ₂₃ N ₃ O ₃

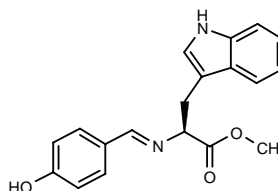
SOURCE – AstraZeneca.

REFERENCES

1. Tucker, H. et al. (AstraZeneca plc; AstraZeneca AB) *Cpds. and their use as cysteine protease inhibitors.* WO 0130772.

304701

N-(4-Hydroxybenzylidene)-L-tryptophan methyl ester



C19 H18 N2 O3; Mol wt: 322.3622

ACTION – A representative compound from a series of optionally substituted Schiff base condensation products and the carba analogues thereof with macrophage migration-inhibitory factor (MIF)-antagonist activity, potentially useful for the treatment or prevention of cancer, immune, autoimmune and inflammatory disorders such as arthritis, proliferative vascular disease, acute respiratory distress syndrome, cytokine-mediated toxicity, septic shock, psoriasis, asthma, insulin-dependent diabetes, multiple sclerosis, graft-versus-host disease and lupus. *In vitro*, compound inhibited MIF tautomerase activity using L-dopachrome methyl ester as the substrate with an IC_{50} value of 5 μ M. In addition, it was shown to inhibit MIF-induced proliferation of quiescent NIH/3T3 cells, being equipotent to an anti-MIF monoclonal antibody, as well as to antagonize the protective effects of recombinant MIF against apoptosis induced by serum withdrawal in cultured NIH/3T3 cells at 10 μ M.

SOURCE – Picower Institute for Medical Research, Manhasset, NY (US).

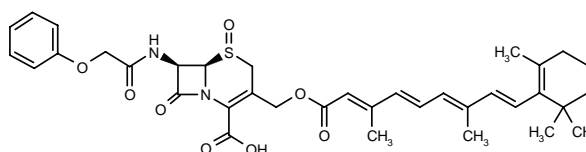
REFERENCES

1. Al-Abed, Y. and Bucala, R. (Picower Institute for Medical Research) *Cpds. having MIF antagonist activity.* WO 0132606.

307037

*O*¹⁵-[(6*R*,7*R*)-2-Carboxy-5-oxido-8-oxo-7-(2-phenoxyacetamido)-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-ylmethyl]retinoic acid

Retinoic acid (6*R*,7*R*)-4-carboxy-1-oxo-7-(2-phenoxyacetamido)cephem-3-ylmethyl ester



C36 H42 N2 O8 S; Mol wt: 662.7998

ACTION – Enzyme-activatable prodrug, a conjugate of *all-trans*-retinoic acid (ATRA) and an oxocephem that is rapidly hydrolyzed by monoclonal antibody-conjugated β -lactamase to active compounds and shows comparable cytotoxic activity to ATRA against murine leukemia L1210 and P388 cells, sarcoma S-180, human breast carcinoma MCF-7 and human leukemia MOLT-4 and CEM cells, but is less toxic both *in vitro* in normal lung cells and *in vivo* in mice (LD_{50} = 170 and 95 mg/kg s.c. for prodrug and ATRA, respectively). In addition, compound inhibited squamous metaplasia and keratinization in tracheal organ cultures derived from vitamin A-deficient hamsters. Potentially useful for the prevention of skin, bladder and breast cancer.

SOURCES – Academia Sinica, Taipei (TW); Shiraz University, Shiraz (IR); University of Tehran, Tehran (IR).

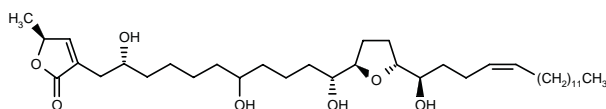
REFERENCES

1. Hakimelahi, G.H. et al. *Design and synthesis of a cephalosporin-retinoic acid prodrug activated by a monoclonal antibody-beta-lactamase conjugate*. Bioorg Med Chem 2001, 9(8): 2139.

ANNOCHERIMOLIN

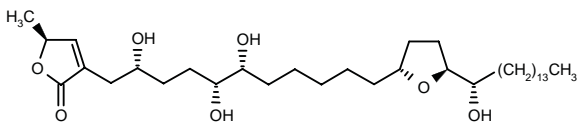
305744

5(S)-Methyl-3-[2(R),7,11(R)-trihydroxy-11-[5(R)-[1(R)-hydroxy-4(Z)-heptadecenyl]tetrahydrofuran-2(R)-yl]-undecyl]furan-2(5H)-one



C37 H66 O7; Mol wt: 622.9214

ACTION – Cytotoxic agent extracted from the seeds of the tropical tree *Annona cherimolia*, with strong cytotoxic activity against human breast carcinoma MCF-7, colon carcinoma HT-29 and human prostate cancer PC-3 cells, where it showed 100-10,000-fold greater potency than doxorubicin. Another related compound is:



Annomolin [305743]: C35 H64 O7

SOURCES – Catholic University of Daegu, Gyeongsan (KR); Yeungnam University, Gyeongsan (KR).

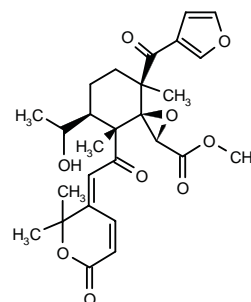
REFERENCES

1. Kim, D.H. et al. *Annomolin and annocheriminol, new cytotoxic annonaceous acetogenins from Annona cherimolia seeds*. J Nat Prod 2001, 64(4): 502.

HAPERFORINE B1^{1,2}

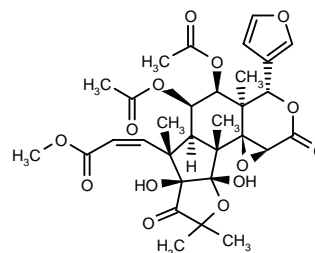
304592

(2S,3R,4R,5S,8R)-4-[(E)-2-(2,2-Dimethyl-6-oxo-3,6-dihydro-2H-pyran-3-ylidene)acetyl]-8-(furan-3-ylcarbonyl)-5-[1(R)-hydroxyethyl]-4,8-dimethyl-1-oxaspiro[2.5]octane-2-carboxylic acid methyl ester

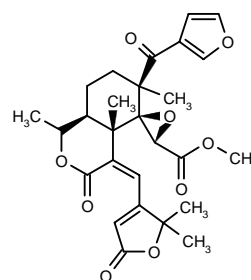


C27 H32 O9; Mol wt: 500.5408

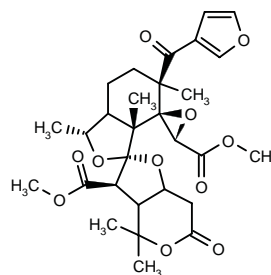
ACTION – Agent for the treatment of cancer and malaria isolated from extracts of plants of the genus *Harrisonia*, particularly *Harrisonia perforata*, proven to concentration-dependently inhibit the proliferation of human glioblastoma A-172, U-373 and U-87, non-small cell lung carcinoma A549 and colorectal carcinoma HCT-15 and LoVo cells at 1.0-100.0 μ g/ml. Other compounds from this series of limonoid derivatives are:



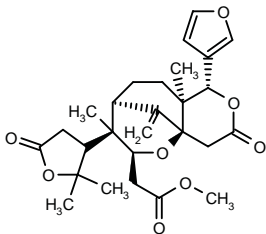
Haperforine A^{1,3,5} [304593]: C31 H36 O14



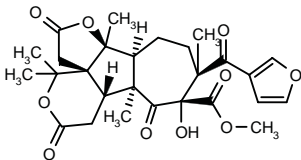
Haperforine B¹ [304594]: C27 H30 O9



Haperforine C¹ [304595]: C29 H36 O11



Haperforine E^{1,3} [304596]: C27 H34 O



Haperforine F^{1,4} [304597]: C27 H32 O10

SOURCE – CNRS.

REFERENCES

1. Potier, P.J.-P. et al. (CNRS [Centre National de la Recherche Scientifique]) *Novel limonoids for use particularly in the treatment of cancer and method for producing the same*. FR 2800075, WO 0130776.

2. Chiaroni, A. et al. *New limonoids from Harrisonia perforata (Blanco) Merr.* Acta Crystallograph Sect C. 2000, C56(6): 711.

3. Khuong-Huu, Q. et al. *New rearranged limonoids from Harrisonia perforata*. J Nat Prod 2000, 63(7): 1015.

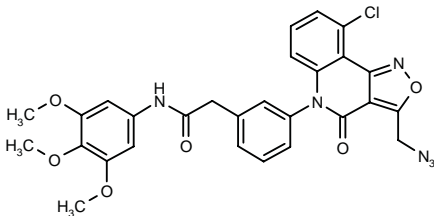
4. Khuong-Huu, Q. et al. *New rearranged limonoids from Harrisonia perforata III*. J Nat Prod 2001, 64(5): 634.

5. Rajab, M.S. et al. *11β,12β-Diacetoxyharrisonin, a tetranortriterpenoid from Harrisonia abyssinica*. Phytochemistry 1999, 52(1): 127.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

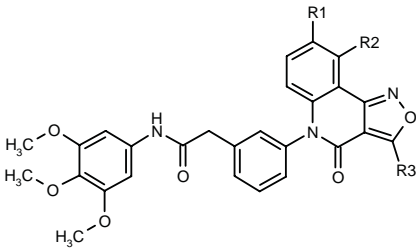
303881

2-[3-[3-(Azidomethyl)-9-chloro-4-oxo-4,5-dihydroisoxazolo[4,3-*c*]quinolin-5-yl]phenyl]-*N*-(3,4,5-trimethoxyphenyl)acetamide



C28 H23 Cl N6 O6; Mol wt: 574.9787

ACTION – Multidrug resistance protein (MRP1) inhibitor, potentially useful for the treatment of MRP1-conferred multidrug resistance (MDR) in resistant neoplasms. Other exemplified tricyclic compounds include the following:



Compound	R1	R2	R3	Formula
303882	H	F	Me	C ₂₈ H ₂₄ FN ₃ O ₆
303883	H	OMe	Me	C ₂₉ H ₂₇ N ₃ O ₇
303884	4-MeO-Ph	H	Me	C ₃₅ H ₃₁ N ₃ O ₇
303885	H	CO ₂ H	Me	C ₂₉ H ₂₆ N ₃ O ₈
303886	H	Cl	NHCH(CH ₂ Ph)CO ₂ Me	C ₃₇ H ₃₃ ClN ₄ O ₈
303887	H	Cl	PhS	C ₃₃ H ₂₆ ClN ₃ O ₆ S
303888	4-CF ₃ -Ph	H	Me	C ₃₈ H ₂₈ F ₃ N ₃ O ₆
303889	H	I	Me	C ₂₈ H ₂₄ IN ₃ O ₆
303890	H	2-thienyl	Me	C ₃₂ H ₂₇ N ₃ O ₆ S
303891	H	Cl	OMe	C ₂₈ H ₂₄ ClN ₃ O ₇

SOURCE – Lilly.

REFERENCES

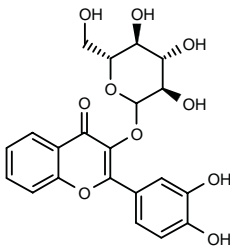
1. Bonjouklian, R. et al. (Eli Lilly and Company) *Cpds. and methods for inhibiting MRP1*. WO 0127116.

CHEMOPROTECTIVE AGENTS

FREDERINE

306778

2-(3,4-Dihydroxyphenyl)-3-(D-glucopyranosyloxy)-4*H*-1-benzopyran-4-one



C21 H20 O10; Mol wt: 432.3790

ACTION – Antioxidant (IC₅₀ = 2.8 nM in rat liver microsomes) with protective effects against doxorubicin-induced cardiotoxicity both *in vitro* (in isolated mouse left atrium) and *in vivo* in mice. Compound did not induce toxicity in hepatocytes and did not reduce the anti-proliferative effect of doxorubicin against human ovarian carcinoma A2780 or OVCAR-3 cells and human breast cancer MCF-7 cells *in vitro*, or in OVCAR-3 xenografts in nude mice. Potentially useful as a cardioprotectant in doxorubicin-treated cancer patients.

SOURCES— Universiteit Maastricht, Maastricht (NL); Vrije Universiteit, Amsterdam (NL).

REFERENCES

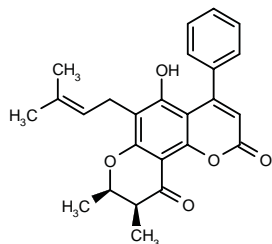
1. Frédérique, A. et al. *Synthesis of novel 3,7-substituted-2-(3',4'-dihydroxyphenyl) flavones with improved antioxidant activity*. J Med Chem 2000, 43(20): 3752.
2. Van Acker, F.A.A. et al. *Frederine, a new and promising protector against doxorubicin-induced cardiotoxicity*. Clin Cancer Res 2001, 7(5): 1378.
3. Van Acker, F.A.A. et al. *New synthetic flavonoids as potent protectors against doxorubicin-induced cardiotoxicity*. Free Radical Biol Med 2001, 31(1): 31.

CHEMOPREVENTIVE AGENTS

CALOCOUMARIN A

306773

5-Hydroxy-8(*R*),9(*S*)-dimethyl-6-(3-methyl-2-butenyl)-4-phenyl-2,8,9,10-tetrahydrobenzo[1,2-*b*:3,4-*b'*]dipyran-2,10-dione



C25 H24 O5; Mol wt: 404.4596

ACTION— Chemopreventive agent, a natural extract from the plant *Calophyllum inophyllum* with *in vitro* inhibitory activity against TPA-induced Epstein-Barr virus early antigen (EBV-EA) activation in Raji cells. *In vivo*, in a two-stage mouse skin carcinogenesis model in mice, where skin papillomas were induced by DMBA and promoted by TPA, compound strongly delayed the appearance and reduced the number of papillomas.

SOURCES— Kyoto Prefectural University of Medicine, Kyoto (JP); Meijo University, Nagoya (JP); National University of Singapore (SG); Tokai Gakuen University (JP).

REFERENCES

1. Ito, C. et al. *Studies on antitumor promoter from tropical medicinal plants (8). Isolation and structure elucidation of new coumarins from Calophyllum species (Guttiferae)*. 119th Annu Meet Pharm Soc Jpn (March 29-31, Tokushima) 1999, Abst 31(PO) 10-040.
2. Itoigawa, M. et al. *Cancer chemopreventive agents, 4-phenylcoumarins from Calophyllum inophyllum*. Cancer Lett 2001, 169(1): 15.

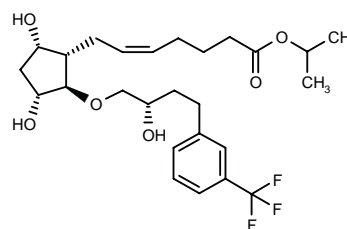
OCULAR MEDICATIONS

AL-16049*

278361

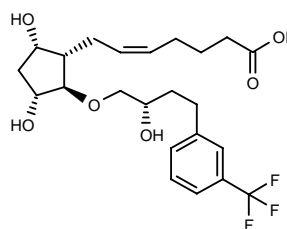
7-[(1*S*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[2(*S*)-hydroxy-4-[3-(trifluoromethyl)phenyl]butoxy]cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

17-[3-(Trifluoromethyl)phenyl]-13,14-dihydro-18,19,20-trinor-13-oxaprostaglandin F_{2α} isopropyl ester



C26 H37 F3 O6; Mol wt: 502.5663

ACTION— Antiglaucoma agent, the isopropyl ester prodrug of the 13-oxaprostaglandin **AL-16082**, a potent FP agonist (EC₅₀ = 1.8 nM for agonist activity in 3T3 fibroblasts; K_i = 790 nM for FP receptor affinity in bovine corpus luteum). This prodrug significantly lowered intraocular pressure (IOP) in ocular hypertensive monkeys after ocular application, inducing a maximum reduction of 30% with minimal side effects.



AL-16082 [307453]: C23 H31 F3 O6

SOURCE— Alcon.

REFERENCES

1. Feng, Z. and Hellberg, M.R. (Alcon Laboratories, Inc.) *13-Oxa prostaglandins for the treatment of glaucoma and ocular hypertension*. US 6232344, WO 9932441.
2. Feng, Z. et al. *Design and synthesis of 13-oxa prostaglandin analogs as antiglaucoma agents*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 236.

*Identified compound **278361** (see **278360**) Drug Data Rep 1999, 021(08): 0743.

SOURCES— Universiteit Maastricht, Maastricht (NL); Vrije Universiteit, Amsterdam (NL).

REFERENCES

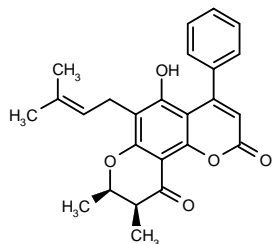
1. Frédérique, A. et al. *Synthesis of novel 3,7-substituted-2-(3',4'-dihydroxyphenyl) flavones with improved antioxidant activity*. J Med Chem 2000, 43(20): 3752.
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3. Van Acker, F.A.A. et al. *New synthetic flavonoids as potent protectors against doxorubicin-induced cardiotoxicity*. Free Radical Biol Med 2001, 31(1): 31.

CHEMOPREVENTIVE AGENTS

CALOCOUMARIN A

306773

5-Hydroxy-8(*R*),9(*S*)-dimethyl-6-(3-methyl-2-butenyl)-4-phenyl-2,8,9,10-tetrahydrobenzo[1,2-*b*:3,4-*b'*]dipyran-2,10-dione



C25 H24 O5; Mol wt: 404.4596

ACTION— Chemopreventive agent, a natural extract from the plant *Calophyllum inophyllum* with *in vitro* inhibitory activity against TPA-induced Epstein-Barr virus early antigen (EBV-EA) activation in Raji cells. *In vivo*, in a two-stage mouse skin carcinogenesis model in mice, where skin papillomas were induced by DMBA and promoted by TPA, compound strongly delayed the appearance and reduced the number of papillomas.

SOURCES— Kyoto Prefectural University of Medicine, Kyoto (JP); Meijo University, Nagoya (JP); National University of Singapore (SG); Tokai Gakuen University (JP).

REFERENCES

1. Ito, C. et al. *Studies on antitumor promoter from tropical medicinal plants (8). Isolation and structure elucidation of new coumarins from Calophyllum species (Guttiferae)*. 119th Annu Meet Pharm Soc Jpn (March 29-31, Tokushima) 1999, Abst 31(PO) 10-040.
2. Itoigawa, M. et al. *Cancer chemopreventive agents, 4-phenylcoumarins from Calophyllum inophyllum*. Cancer Lett 2001, 169(1): 15.

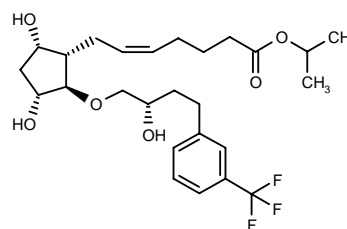
OCULAR MEDICATIONS

AL-16049*

278361

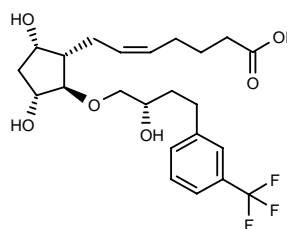
7-[(1*S*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[2(*S*)-hydroxy-4-[3-(trifluoromethyl)phenyl]butoxy]cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

17-[3-(Trifluoromethyl)phenyl]-13,14-dihydro-18,19,20-trinor-13-oxaprostaglandin F_{2α} isopropyl ester



C26 H37 F3 O6; Mol wt: 502.5663

ACTION— Antiglaucoma agent, the isopropyl ester prodrug of the 13-oxaprostaglandin **AL-16082**, a potent FP agonist (EC₅₀ = 1.8 nM for agonist activity in 3T3 fibroblasts; K_i = 790 nM for FP receptor affinity in bovine corpus luteum). This prodrug significantly lowered intraocular pressure (IOP) in ocular hypertensive monkeys after ocular application, inducing a maximum reduction of 30% with minimal side effects.



AL-16082 [307453]: C23 H31 F3 O6

SOURCE— Alcon.

REFERENCES

1. Feng, Z. and Hellberg, M.R. (Alcon Laboratories, Inc.) *13-Oxa prostaglandins for the treatment of glaucoma and ocular hypertension*. US 6232344, WO 9932441.
2. Feng, Z. et al. *Design and synthesis of 13-oxa prostaglandin analogs as antiglaucoma agents*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 236.

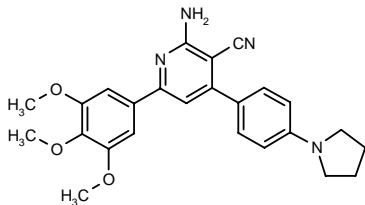
*Identified compound **278361** (see **278360**) Drug Data Rep 1999, 021(08): 0743.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

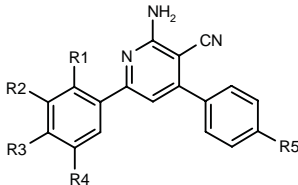
303566

2-Amino-4-[4-(1-pyrrolidinyl)phenyl]-6-(3,4,5-trimethoxyphenyl)pyridine-3-carbonitrile



C25 H26 N4 O3; Mol wt: 430.5054

ACTION – An inhibitor of osteoclast vacuolar H⁺-ATPase, with potential for the treatment or prevention of osteoporosis, Paget’s disease, hyperparathyroidism, periodontal diseases, prosthesis- and/or implant-related bone loss, tumors, AIDS, Alzheimer’s disease, angiogenesis, rheumatoid arthritis, diabetic retinopathy, psoriasis and diabetes. Other specifically claimed compounds from this series of nicotinonitrile derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
303568	H	OMe	OMe	OMe	t-Bu	C ₂₅ H ₂₇ N ₃ O ₃
303569	H	OMe	OMe	OMe	OEt	C ₂₃ H ₂₃ N ₃ O ₄
303570	H	OMe	OMe	H	O(CH ₂) ₃ N(Me) ₂	C ₂₅ H ₂₆ N ₄ O ₃
303571	OEt	H	H	H	N(Me) ₂	C ₂₂ H ₂₂ N ₄ O
303572	OMe	H	OMe	H	N(Me) ₂	C ₂₂ H ₂₂ N ₄ O ₂
303573	H	OMe	OMe	OMe	i-Pr	C ₂₄ H ₂₅ N ₃ O ₃

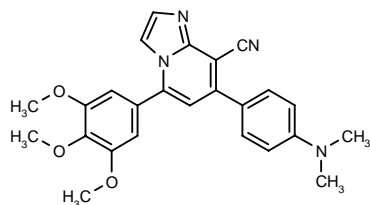
SOURCE – AstraZeneca.

REFERENCES

1. Herslöf, M. and Sörensen, H. (AstraZeneca AB) *Novel nicotinonitrile cpds.* WO 0125207.

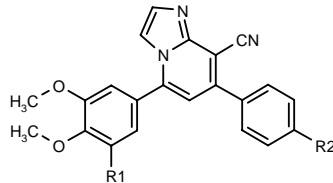
303575

7-[4-(Dimethylamino)phenyl]-5-(3,4,5-trimethoxyphenyl)-imidazo[1,2-a]pyridine-8-carbonitrile



C25 H24 N4 O3; Mol wt: 428.4896

ACTION – An inhibitor of osteoclast vacuolar H⁺-ATPase, with potential for the treatment or prevention of osteoporosis, Paget’s disease, hyperparathyroidism, periodontal diseases, prosthesis- and/or implant-related bone loss, tumors, AIDS, Alzheimer’s disease, angiogenesis, rheumatoid arthritis, diabetic retinopathy, psoriasis and diabetes. Other specifically claimed compounds from this series of imidazopyridine carbonitrile derivatives are:



Compound	R1	R2	Formula
303576	H	OMe	C ₂₃ H ₁₉ N ₃ O ₃
303577	OMe	1-pyrrolidinyl	C ₂₇ H ₂₆ N ₄ O ₃

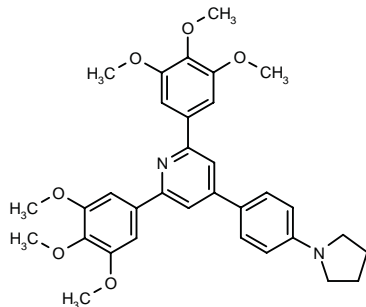
SOURCE – AstraZeneca.

REFERENCES

1. Herslöf, M. et al. (AstraZeneca AB) *Novel imidazopyridine carbonitrile cpds.* WO 0125237.

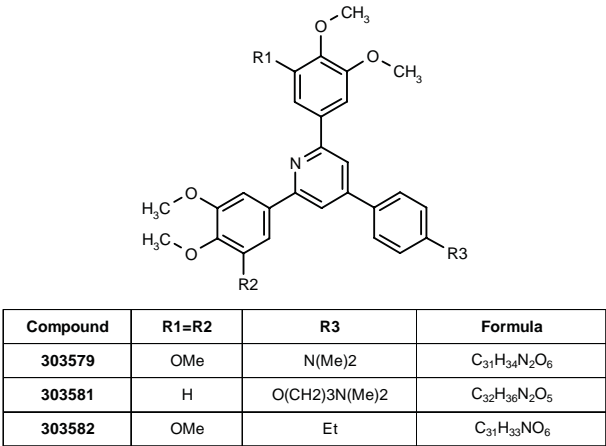
303578

4-[4-(1-Pyrrolidinyl)phenyl]-2,6-bis(3,4,5-trimethoxyphenyl)pyridine



C33 H36 N2 O6; Mol wt: 556.6554

ACTION – An inhibitor of osteoclast vacuolar H⁺-ATPase, with potential for the treatment or prevention of osteoporosis, Paget’s disease, hyperparathyroidism, periodontal diseases, prosthesis- and/or implant-related bone loss, tumors, AIDS, Alzheimer’s disease, angiogenesis, rheumatoid arthritis, diabetic retinopathy, psoriasis and diabetes. Other specifically claimed compounds from this series of trisubstituted pyridine derivatives are:



SOURCE – AstraZeneca.

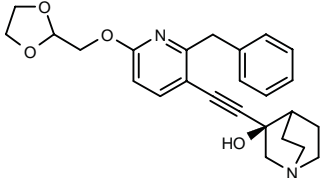
REFERENCES

1. Herslöf, M. et al. (AstraZeneca AB) *Novel trisubst. pyridine cpds.* WO 0125204.

TREATMENT OF LIPOPROTEIN DISORDERS

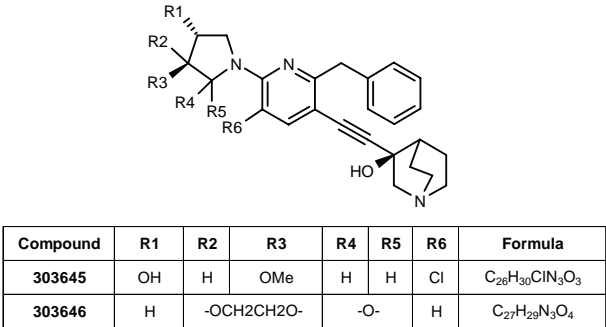
303644

3(R)-[2-[2-Benzyl-6-(1,3-dioxolan-2-ylmethoxy)pyridin-3-yl]ethynyl]quinuclidin-3-ol



C25 H28 N2 O4; Mol wt: 420.5062

ACTION – Agent for the treatment of hyperlipidemia, atherosclerosis and ischemic cardiopathy, an inhibitor of squalene synthase (IC₅₀ = 11 nM in rat hepatic microsomes). In addition, compound was shown to inhibit cholesterol (IC₅₀ = 0.055 μM) and triglyceride (85% inhibition at 1 μM) biosynthesis *in vitro* in rat hepatic cells, and cholesterol biosynthesis *in vivo* in rats (82% inhibition at 1 mg/kg p.o.). Other exemplified compounds from this series of quinuclidine derivatives include the following:



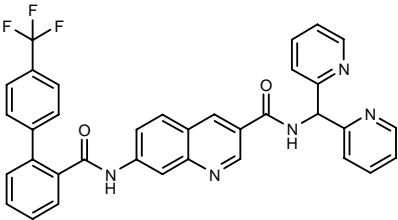
SOURCE – Eisai.

REFERENCES

1. Okada, T. et al. (Eisai Co., Ltd.) *Quinuclidine cpds. and drugs containing the same as the active ingredient.* WO 0123383.

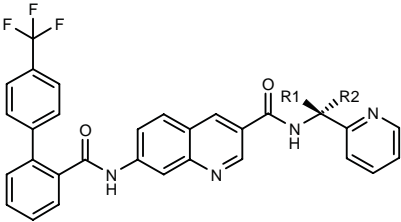
304901

N-[Bis(2-pyridyl)methyl]-7-[4'-(trifluoromethyl)biphenyl-2-yl]carboxamido]quinoline-3-carboxamide



C35 H24 F3 N5 O2; Mol wt: 603.6016

ACTION – Agent that inhibits the secretion of apolipo-protein B and/or microsomal triglyceride transfer protein (MTP), with potential for the treatment of obesity, atherosclerosis, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hypoalphalipoproteinemia, pancreatitis, diabetes, myocardial infarction, stroke, restenosis and syndrome X. Other specifically claimed compounds are:



Compound	R1	R2	Formula
304902	Ph	H	C ₃₆ H ₂₅ F ₃ N ₄ O ₂
304903	Me	Me	C ₃₂ H ₂₅ F ₃ N ₄ O ₂
304904	H	Ph	C ₃₆ H ₂₅ F ₃ N ₄ O ₂
304905	Et	H	C ₃₂ H ₂₅ F ₃ N ₄ O ₂
304906	H	Et	C ₃₂ H ₂₅ F ₃ N ₄ O ₂

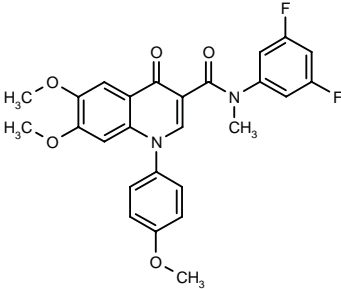
SOURCE – Pfizer.

REFERENCES

1. Bertinato, P. et al. (Pfizer Products Inc.) 7-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)amino]-quinoline-3-carboxylic acid amides, and methods of inhibiting the secretion of apolipoprotein B. EP 1099701, JP 2001139555.

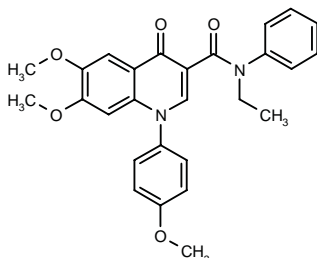
304963

N-(3,5-Difluorophenyl)-6,7-dimethoxy-1-(4-methoxyphenyl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide



C26 H22 F2 N2 O5; Mol wt: 480.4648

ACTION – Ileal bile acid transport inhibitor that produced a 55.3% inhibition of ileal bile acid transporter activity at 30 µg/ml p.o. in hamster everted ileal rings. As such, this compound is indicated for the treatment of hyperlipidemia and atherosclerosis. Another exemplified 1,4-dihydroquinoline derivative is:



304964: C₂₇ H₂₆ N₂ O₅

SOURCE – Sankyo.

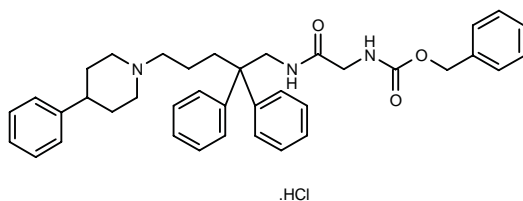
REFERENCES

1. Kurata, H. et al. (Sankyo Co., Ltd.) *Nitrogenous heterocycle derivs.* JP 2001199965, WO 0134570.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

303722

N-[2-[2,2-Diphenyl-5-(4-phenylpiperidin-1-yl)pentyl-amino]-2-oxoethyl]carbamic acid benzyl ester hydrochloride



C₃₈ H₄₃ N₃ O₃ . HCl; Mol wt: 626.2366

ACTION – Melanin-concentrating hormone (MCH) antagonist (IC₅₀ = 5 nM in a [³⁵S]-GTPγ binding assay using SLC-1-expressing CHO cells), potentially useful for the treatment of various types of obesity, as well as hyperphagia and malignant or systemic mastocytosis. A representative compound from a series of diaryl derivatives.

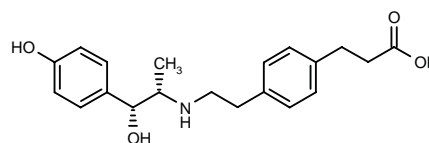
SOURCE – Takeda.

REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *MCH antagonists.* WO 0121169.

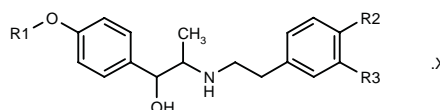
304912

3-[4-[2-[2(*R*)-Hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methyl-ethylamino]ethyl]phenyl]propionic acid



C₂₀ H₂₅ N O₄; Mol wt: 343.4205

ACTION – Potent and selective β₃-adrenoceptor agonist, as demonstrated in functional assays by EC₅₀ values of 17 nM, 4.9 µM and 0.39 µM for stimulation of β₃-adrenoceptors in ferret bladder smooth muscle, β₁-adrenoceptors in rat atrium and β₂-adrenoceptors in pregnant rat uterus, respectively. No mortality was observed following a single dose of 400 mg/kg i.v. to mice. Potentially useful for the treatment or prevention of obesity, hyperglycemia, intestinal hypermotility, pollakiuria, urinary incontinence, depression, gallstones and biliary tract hypermotility. Other compounds from this series of 2-aminopropanol derivatives include the following:



Compound	R1	R2	R3	Isomer	X	Formula
304914	H	(CH ₂) ₄ CO ₂ Et	H	1R*,2S*	HCl	C ₂₄ H ₃₃ NO ₄ .HCl
304915	H	(CH ₂) ₄ CO ₂ H	H	1R*,2S*		C ₂₂ H ₂₉ NO ₄
304916	Na	CH ₂ CH ₂ CO ₂ Na	H	1R*,2S*		C ₂₀ H ₂₃ NNa ₂ O ₄
304917	Na	CO ₂ Na	H	1R*,2S*		C ₁₈ H ₁₉ NNa ₂ O ₄
304919	Na	(E)-CH=CHCO ₂ Na	H	1R*,2S*		C ₂₀ H ₂₁ NNa ₂ O ₄
304921	H	(CH ₂) ₃ CO ₂ H	H	1R*,2S*		C ₂₁ H ₂₇ NO ₄
304922	H	CH ₂ CH ₂ CO ₂ H	Cl	1S,2R		C ₂₀ H ₂₄ ClNO ₄
304923	H	(E)-CH=CHCO ₂ H	Cl	1S,2R		C ₂₀ H ₂₂ ClNO ₄

SOURCE – Kissei.

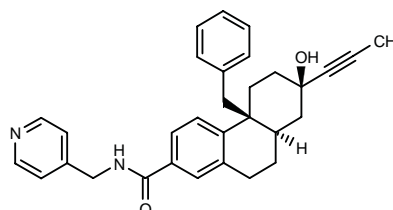
REFERENCES

1. Tamai, T. et al. (Kissei Pharmaceutical Co., Ltd.) *2-Aminopropanol derivs.* JP 2001114736.

CP-472555*

296893

(4*b*S,7*R*,8*a**R*)-4*b*-Benzyl-7-hydroxy-7-(1-propynyl)-*N*-(4-pyridinylmethyl)-4*b*,5,6,7,8,8*a*,9,10-octahydrophenanthrene-2-carboxamide



C₃₁ H₃₂ N₂ O₂; Mol wt: 464.6058

ACTION – Selective orally active nonsteroidal glucocorticoid receptor antagonist proven to reduce food intake and decrease glucose levels in *ob/ob* mice. Potentially useful for the treatment of obesity and diabetes.

SOURCE – Pfizer.

REFERENCES

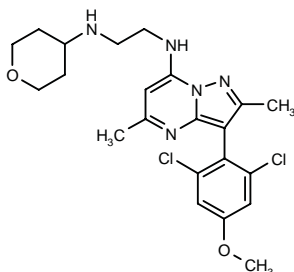
1. Chen, Y.L. and Hamanaka, E.S. (Pfizer Products Inc.) *Use of corticotropin releasing factor antagonists for treating syndrome X*. EP 1097709.
2. Dow, R.L. et al. (Pfizer Products Inc.) *Glucocorticoid receptor modulators*. WO 0066522.
3. Liu, K.K.-C. et al. *Novel, selective non-steroidal glucocorticoid receptor modulators (SGRM's) for the treatment of obesity*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 169.

*Identified compound **296893** Drug Data Rep 2001, 023(04): 0418.

CP-671906-01

307492

N-[3-(2,6-Dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-7-yl]-*N'*-(tetrahydro-2*H*-pyran-4-yl)ethane-1,2-diamine



C22 H27 Cl2 N5 O2; Mol wt: 464.3943

ACTION – Potent and selective neuropeptide Y (NPY) Y_1 receptor antagonist ($K_i = 4$ nM in SK-N-MC cells; $K_b = 26$ nM in rabbit vas deferens) proven to completely inhibit the NPY-induced blood pressure increase in rats at 3 mg/kg i.v. Compound was found to inhibit food intake in animal models. Potentially useful for the treatment of obesity.

SOURCES – Neurogen; Pfizer.

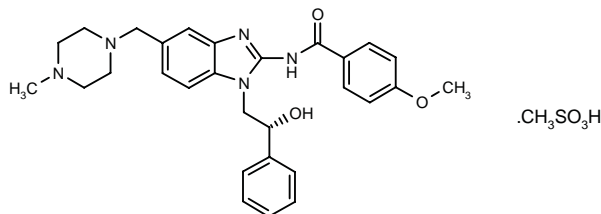
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1. Darrow, J.W. et al. (Neurogen Corp.;Pfizer Inc.) *Certain alkylene diamine-substd. pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines*. WO 0123387.
2. Griffith, D.A. et al. *Structure-activity relationships within a series of pyrazolo-pyrimidine NPY-Y1 receptor antagonists*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 283.

GW-569180A

307438

N-[1-[2(*R*)-Hydroxy-2-phenylethyl]-5-(4-methylpiperazin-1-ylmethyl)-1*H*-benzimidazol-2-yl]-4-methoxybenzamide mesylate



C29 H33 N5 O3 . C H4 O3 S; Mol wt: 595.7173

ACTION – Neuropeptide Y (NPY) Y_5 receptor antagonist ($IC_{50} = 24$ nM for human Y_5 receptors) with good solubility and cell membrane permeability. Potentially useful for the treatment of obesity.

SOURCE – GlaxoSmithKline.

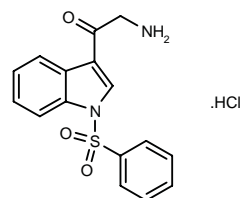
REFERENCES

1. Fang, J. et al. *2-Aminobenzimidazole as neuropeptideY Y5 antagonists: Solution phase synthesis and structure-activity relationships*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 26.
2. Heyer, D. et al. *2-Aminobenzimidazoles: A class of orally bioavailable and brain permeable neuropeptide YY5 antagonists*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 284.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

304935

2-Amino-1-[1-(phenylsulfonyl)-1*H*-indol-3-yl]ethanone hydrochloride



C16 H14 N2 O3 S . HCl; Mol wt: 350.8245

ACTION – Agent with affinity for the thrombopoietin (TPO) receptor, potentially useful for the treatment of thrombocytopenia and for modulating the production of platelets.

SOURCES – Nippon Chemical Research; Torii.

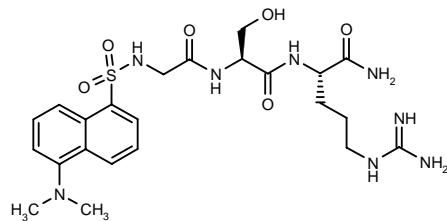
REFERENCES

1. Murakami, Y. et al. (Torii Pharmaceutical Co., Ltd.;Nippon Chemical Research) *Cpds. with affinity for thrombopoietin receptor*. JP 2001097948.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

303673

N-[5-(Dimethylamino)naphthalen-1-ylsulfonyl]glycyl-L-seryl-L-argininamide



C23 H34 N8 O6 S; Mol wt: 550.6376

ACTION – Neuropeptide FF analogue with micromolar affinity for the neuropeptide FF receptor ($K_i = 1.4 \mu\text{M}$) and predicted to penetrate the blood–brain barrier. Potentially useful for the treatment of opiate withdrawal.

SOURCE – University of Florida, Gainesville, FL (US).

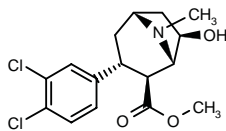
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O-1924^{3,4}

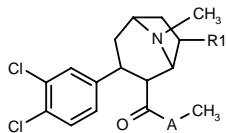
305909

(1*S*,2*S*,3*R*,5*R*,7*R*)-3-(3,4-Dichlorophenyl)-7-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C16 H19 Cl2 N O3; Mol wt: 344.2361

ACTION – High-affinity ligand for the dopamine transporter ($\text{IC}_{50} = 0.76 \text{ nM}$) with high selectivity versus the 5-HT transporter ($\text{IC}_{50} = 1220 \text{ nM}$), potentially useful for the treatment of cocaine addiction. Other related compounds are:



Compound	R1	A	Isomer	Formula
O-1945 [305910] ^{3,4}	OH	O	1 <i>S</i> ,2 <i>S</i> ,3 <i>S</i> ,5 <i>R</i> ,7 <i>R</i>	C ₁₆ H ₁₉ Cl ₂ NO ₃
O-1157 [305911] ^{1,2,4}	H	O	1 <i>R</i> ,2 <i>S</i> ,3 <i>R</i> ,5 <i>S</i>	C ₁₆ H ₁₉ Cl ₂ NO ₂
O-2099 [306148] ⁴	OH	CH2	1 <i>S</i> *,2 <i>S</i> *,3 <i>R</i> *,5 <i>R</i> *,7 <i>R</i> *	C ₁₇ H ₂₁ Cl ₂ NO ₂

SOURCE – Organix.

REFERENCES

1. Meltzer, P.C. et al. *2-Carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes; Potent non-nitrogen inhibitors of monoamine transporters.* J Med Chem 1997, 40(17): 2661.

2. Meltzer, P.C. et al. *Bicyclo[3.2.1]octanes: Synthesis and inhibition of binding at the dopamine and serotonin transporters.* Bioorg Med Chem Lett 1999, 9(6): 857.

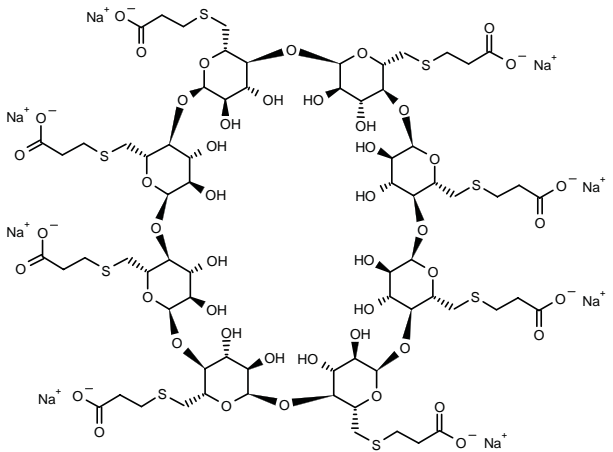
3. Meltzer, P.C. et al. *Structure activity relationships of inhibition of the dopamine transporter by 3-arylbicyclo[3.2.1]octanes.* Med Chem Res 1998, 8(1-2): 12.

4. Meltzer, P.C. et al. *Synthesis of 6- and 7-hydroxy-8-azabicyclo[3.2.1]octanes and their binding affinity for the dopamine and serotonin transporters.* J Med Chem 2001, 4(16): 2619.

ORG-25969

306386

6*A*,6*B*,6*C*,6*D*,6*E*,6*F*,6*G*,6*H*-Octakis-*S*-(2-carboxyethyl)-6*A*,6*B*,6*C*,6*D*,6*E*,6*F*,6*G*-octasulfanyl- γ -cyclodextrin octa-sodium salt



C72 H104 Na8 O48 S8; Mol wt: 2178.0140

ACTION – Synthetic cyclodextrin proven to rapidly and efficiently complex with rocuronium and reverse its neuromuscular blocking effects, in the absence of cardiovascular side effects.

SOURCE – Akzo Nobel.

REFERENCES

1. Zhang, M. et al. (Akzo Nobel N.V.) *6-Mercapto-cyclodextrin derivs: Reversal agents for drug-induced neuromuscular block.* WO 0140316.

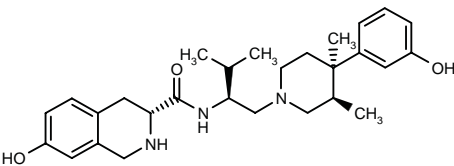
2. Zhang, M.-Q. et al. *Chemical chelation as a novel method of NMB reversal: Discovery of a synthetic cyclodextrin Org 25969.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 307.

RTI-JDTic

306770

7-Hydroxy-*N*-[1 (*S*)-[4 (*R*)-(3-hydroxyphenyl)-3 (*R*),4-dimethylpiperidin-1-ylmethyl]-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxamide

JDTic



C28 H39 N3 O3; Mol wt: 465.6413

ACTION – Potent and selective ligand for the κ opioid receptor (K_i = 0.32, 3.73 and 301 nM for kappa, mu and delta opioid receptors, respectively) with *in vitro* functional antagonist activity in the [35 S]GTP- γ assay (K_i = 0.006 nM for kappa-antagonist potency vs. 3.42 and > 100 nM for mu- and delta-antagonist potency, respectively). Potentially useful for the treatment of substance abuse.

SOURCES – Lilly; Research Triangle Institute, Research Triangle Park, NC (US).

REFERENCES

1. Lu, Y.F. et al. *Studies with the human κ opioid receptor suggest heterogeneity of agonist and antagonist binding domains.* Soc Neurosci Abst 2000, 26(Part 1): Abst 342.9.

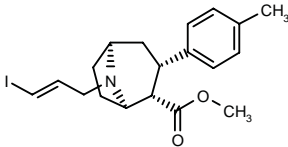
2. Thomas, J.B. et al. *Identification of the first trans-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine derivative to possess highly potent and selective opioid kappa receptor antagonists activity.* J Med Chem 2001, 44(17): 2687.

DIAGNOSTIC AGENTS

PE2I

251264

(1*R*,2*S*,3*S*,5*S*)-8-[3-Iodo-2(*E*)-propenyl]-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C19 H24 I N O2; Mol wt: 425.3036

ACTION – Potent and selective inhibitor of the neuronal dopamine transporter, a cocaine derivative with respective K_i values of 30, 960 and 295 nM for the dopamine, 5-HT and noradrenaline transporters. Experiments using the [123 I]- or [125 I]-radiolabeled forms of compound showed that it selectively recognized the dopamine transporter on both rat striatal and cortical membranes; autoradiographic experiments on brain sections showed intense binding in basal ganglia and low binding in substantia nigra. PET studies in human, using the [11 C]-radiolabeled form of compound demonstrated that it accumulates in a caudate and putamen with a ratio to cerebellum of about 10 at a peak equilibrium (40-50 min) compared to the thalamus/cerebellum ratio of 1.5 at peak equilibrium (20 min). Other human studies using the iodinated form of compound demonstrated that it may be suitable for dynamic SPECT scanning of both cortical and striatal dopamine transporters. Potentially useful as a diagnostic agent for Parkinson's disease.

SOURCE – CIS Bio International (Schering AG).

REFERENCES

1. Mauclaire, L. et al. (CIS Bio International) *Tropane derivs. useable in particular for in vivo detection of dopamine transporters.* EP 0901491, JP 2000510141, US 6180083, WO 9743285.

2. Chalon, S. et al. *Pharmacological characterization of (E)-N-(3-iodoprop-2-enyl)-2 β -carbomethoxy-3 β -(4'-methylphenyl)nortropane as a selective and potent inhibitor of the neuronal dopamine transporter.* J Pharmacol Exp Ther 1999, 291(2): 648.

3. Chalon, S. et al. *Time course of changes in striatal dopamine transporters and D₂ receptors with specific iodinated markers in a rat model of Parkinson's disease.* Synapse 1999, 31(2): 134.

4. Dolle, F. et al. *Highly efficient synthesis of [11 C]PE2I] a selective radioligand for the quantification of the dopamine transporter using PET.* J Label Compd Radiopharm 2000, 43(10): 997.

5. Emond, P. et al. *Synthesis and ligand binding of nortropane derivatives: N-Substituted 2 β -carbomethoxy-3 β -(4'-iodophenyl)nortropane and N-(3-iodotrop-(2E)-enyl)-2 β -carbomethoxy-3 β -(3',4'-disubstituted phenyl)nortropane. New high-affinity and selective compounds for the dopamine transporter.* J Med Chem 1997, 40(9): 1366.

6. Guilloteau, D. et al. *Exploration of the dopamine transporter: In vitro and in vivo characterization of a high-affinity and high-specificity iodinated tropane derivative (E)-N-(3-iodoprop-2-enyl)-2 β -carbomethoxy-3 β -(4'-methylphenyl)nortropane (PE2I).* Nucl Med Biol 1998, 25(4): 331.

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8. Halldin, C. et al. *[11 C]PE2I - A highly selective radioligand for PET-examination of the dopamine transporter in human brain.* 3rd Int Neurorecept Mapp Symp (June 9-11, New York) 2000, Abst.

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13. Pinborg, L.P. et al. *Quantification of [123 I]PE2I binding to the dopamine transporter with SPECT.* 3rd Int Neurorecept Mapp Symp (June 9-11, New York) 2000, Abst.

14. Poyot, T. et al. *Anatomic and biochemical correlates of the dopamine transporter ligand 11 C-PE2I in normal and parkinsonian primates: Comparison with 6-[18 F]fluoro-L-dopa.* J Cereb Blood Flow Metab 2001, 21(7): 782.

15. Repo, E. et al. *Dopamine transporter and D₂-receptor density in late-onset alcoholism.* Psychopharmacology 1999, 147(3): 314.

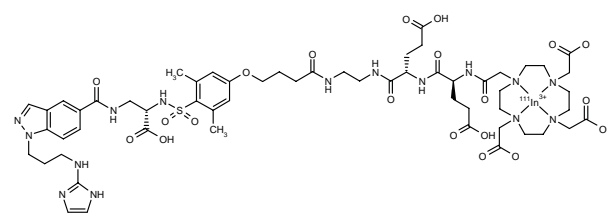
16. Tupala, E. et al. *Dopamine D₂/D₃-receptor and transporter densities in nucleus accumbens and amygdala of type 1 and 2 alcoholics.* Mol Psychiatry 2001, 6(3): 261.

RP-728

307707

[N-[2-[4,7,10-Tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl]-L-glutamyl-N¹-[2-[4-[N-[4-[1(*S*)-carboxy-2-[1-[3-(1*H*-imidazol-2-ylamino)propyl]-1*H*-indazol-5-ylcarboxamido]ethyl]sulfamoyl]-3,5-dimethylphenoxy]butyramido]ethyl]-L- α -glutaminato(3-)]indinyl-111In

TA-103 (as ligand)



C57 H78 In N15 O20 S; Mol wt: 1436.3940

ACTION – Potent and selective ligand for the κ opioid receptor (K_i = 0.32, 3.73 and 301 nM for kappa, mu and delta opioid receptors, respectively) with *in vitro* functional antagonist activity in the [35 S]GTP- γ assay (K_i = 0.006 nM for kappa-antagonist potency vs. 3.42 and > 100 nM for mu- and delta-antagonist potency, respectively). Potentially useful for the treatment of substance abuse.

SOURCES – Lilly; Research Triangle Institute, Research Triangle Park, NC (US).

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1. Lu, Y.F. et al. *Studies with the human κ opioid receptor suggest heterogeneity of agonist and antagonist binding domains.* Soc Neurosci Abst 2000, 26(Part 1): Abst 342.9.

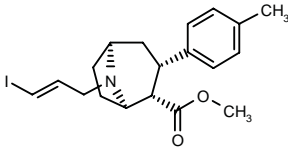
2. Thomas, J.B. et al. *Identification of the first trans-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine derivative to possess highly potent and selective opioid kappa receptor antagonists activity.* J Med Chem 2001, 44(17): 2687.

DIAGNOSTIC AGENTS

PE2I

251264

(1*R*,2*S*,3*S*,5*S*)-8-[3-Iodo-2(*E*)-propenyl]-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C19 H24 I N O2; Mol wt: 425.3036

ACTION – Potent and selective inhibitor of the neuronal dopamine transporter, a cocaine derivative with respective K_i values of 30, 960 and 295 nM for the dopamine, 5-HT and noradrenaline transporters. Experiments using the [123 I]- or [125 I]-radiolabeled forms of compound showed that it selectively recognized the dopamine transporter on both rat striatal and cortical membranes; autoradiographic experiments on brain sections showed intense binding in basal ganglia and low binding in substantia nigra. PET studies in human, using the [11 C]-radiolabeled form of compound demonstrated that it accumulates in a caudate and putamen with a ratio to cerebellum of about 10 at a peak equilibrium (40-50 min) compared to the thalamus/cerebellum ratio of 1.5 at peak equilibrium (20 min). Other human studies using the iodinated form of compound demonstrated that it may be suitable for dynamic SPECT scanning of both cortical and striatal dopamine transporters. Potentially useful as a diagnostic agent for Parkinson’s disease.

SOURCE – CIS Bio International (Schering AG).

REFERENCES

1. Mauclaire, L. et al. (CIS Bio International) *Tropane derivs. useable in particular for in vivo detection of dopamine transporters.* EP 0901491, JP 2000510141, US 6180083, WO 9743285.

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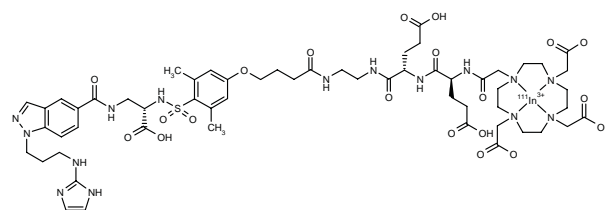
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RP-728

307707

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TA-103 (as ligand)



C57 H78 In N15 O20 S; Mol wt: 1436.3940

ACTION – [^{111}In]-Labeled nonpeptide vitronectin receptor ($\alpha_v\beta_3$) antagonist ($\text{IC}_{50} = 0.2 \text{ nM}$) with moderate selectivity relative to the gpIIb/IIIa receptor ($\text{IC}_{50} = 9 \text{ nM}$). In transgenic mice with mammary tumors, compound (2 mCi/kg i.v.) showed good tumor uptake and rapid clearance from other organs and good-quality images were obtained in this study. The lack of selectivity over the gpIIb/IIIa receptors, however, may preclude its clinical development as a diagnostic for cancer.

SOURCE – DuPont Pharmaceuticals.

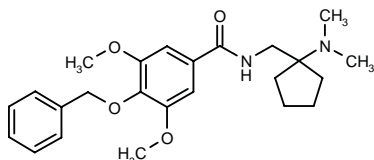
REFERENCES

1. Rajopadhye, M. et al. (DuPont Pharmaceuticals Co.) *Vitronectin receptor antagonist pharmaceuticals*. WO 0035488.
2. Cheesman, E.H. et al. *Nonpeptide vitronectin antagonists labeled with In-111 for imaging tumors*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 88.

PHARMACOLOGICAL TOOLS

306601

4-Benzyloxy-*N*-[1-(dimethylamino)cyclopentylmethyl]-3,5-dimethoxybenzamide



C24 H32 N2 O4; Mol wt: 412.5268

ACTION – Potent and selective inhibitor of the glycine transporter type 2 (GlyT-2; $\text{IC}_{50} = 16 \text{ nM}$) with high selectivity over the GlyT-1 ($\text{IC}_{50} > 100 \text{ nM}$), as well as other biological targets. Compound showed good blood-brain barrier penetration, good stability in plasma and mouse hepatic microsomes, and may be useful as a tool for elucidating the pharmacological role of the GlyT-2 transporter.

SOURCE – Organon.

REFERENCES

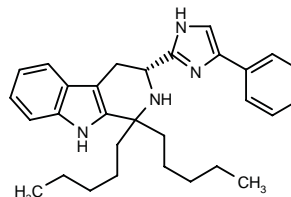
1. Caulfield, W.L. et al. *The first potent and selective inhibitors of the glycine transporter type 2*. J Med Chem 2001, 44(17): 2679.

BN-81674

306504

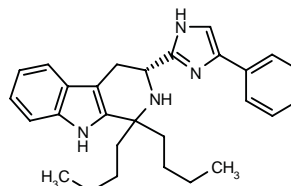
1,1-Dipentyl-3(*R*)-(4-phenyl-1*H*-imidazol-2-yl)-2,3,4,9-tetrahydro-1*H*- β -carboline

1,1-Dipentyl-3(*R*)-(4-phenyl-1*H*-imidazol-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole



C30 H38 N4; Mol wt: 454.6582

ACTION – Nonpeptide high-affinity somatostatin sst_3 ligand ($K_i = 0.92 \text{ nM}$) with high selectivity over sst_1 , sst_2 , sst_4 and sst_5 receptors ($K_i > 10 \mu\text{M}$). Compound acts as a competitive antagonist at human sst_3 receptors expressed in CHO-K1 cells, giving an IC_{50} of 0.84 nM and a K_b value of 2.8 nM. Potentially useful as a pharmacological tool for investigating the physiological role of the sst_3 receptors. Another related compound is:



BN-81644 [306503]: C28 H34 N4

SOURCE – Institut Henri Beaufour.

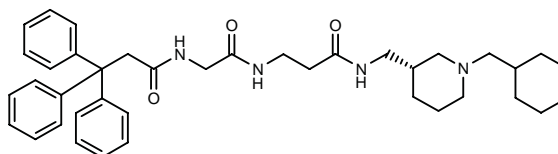
REFERENCES

1. Thuriereau, C.A. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *β -Carboline cpds*. EP 1086101, WO 9964420.
2. Poitout, L. et al. *Identification of potent non-peptide somatostatin antagonists with sst_3 selectivity*. J Med Chem 2001, 44(18): 2990.

CPTP

300770

N-[*N*-[3-[1-(Cyclohexylmethyl)piperidin-3(*R*)-ylmethylamino]-3-oxopropyl]carbamoylethyl]-3,3,3-triphenylpropionamide



C39 H50 N4 O3; Mol wt: 622.8490

ACTION – Potent muscarinic M_3 receptor antagonist with subnanomolar affinity for M_3 receptors ($K_i = 0.31 \text{ nM}$) and high selectivity over other muscarinic receptors (380-, 98- and 45-fold selectivity over M_1 , M_2 and M_4 receptors, respectively). Potentially useful as a pharmacological tool for clarifying the physiological roles of muscarinic M_3 receptors.

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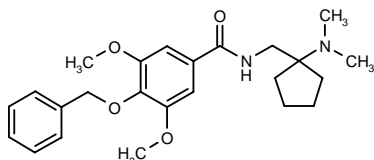
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SOURCE – Organon.

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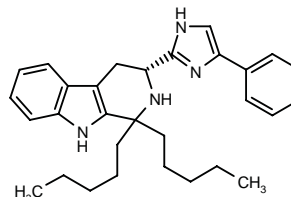
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BN-81674

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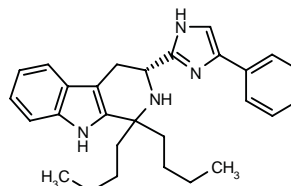
1,1-Dipentyl-3(*R*)-(4-phenyl-1*H*-imidazol-2-yl)-2,3,4,9-tetrahydro-1*H*- β -carboline

1,1-Dipentyl-3(*R*)-(4-phenyl-1*H*-imidazol-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole



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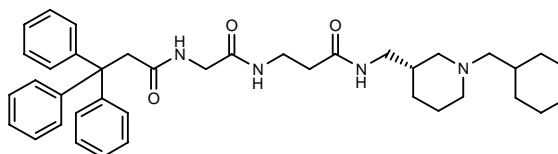
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CPTP

300770

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SOURCE – Banyu.

REFERENCES

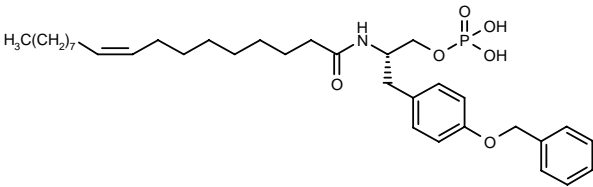
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2. Sagara, Y. et al. *First M3 antagonist (N-cyclohexylmethylpiperidinyltriphenylpropio- amide: CPTP) with a high selectivity over the other receptor subtypes.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 196.

VPC-12249

307744

3-[4-(Benzyloxy)phenyl]-2(*S*)-[9(*Z*)-octadecenamido]prop- yl dihydrogen phosphate



C34 H52 N O6 P; Mol wt: 601.7598

ACTION – Dual lysophosphatidic acid Ip_{A1} (edg2) and Ip_{A3} (edg7) receptor antagonist (K_i = 130 and 428 nM, respectively, in the [³⁵S]GTP-γ binding assay), potentially useful for elucidating the physiological role of LPA receptors.

SOURCE – University of Virginia, Charlottesville, VA (US).

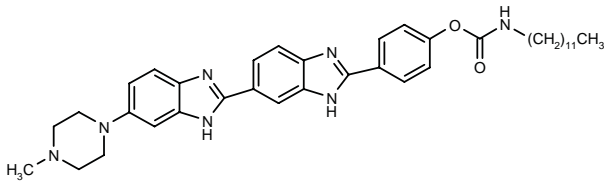
REFERENCES

1. Santos, W.L. et al. *Structure-activity relationships of lysophosphatidic acid: Synthesis and analysis of EDG receptor agonists and antagonists.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 272.

PHARMACEUTICAL AIDS

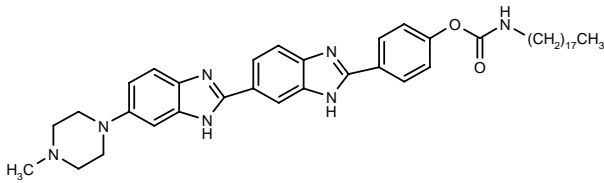
304928

N-Dodecylcarbamic acid 4-[6-(4-methylpiperazin-1-yl)- 1*H*,1'*H*-2,6'-bibenzimidazol-2'-yl]phenyl ester



C38 H49 N7 O2; Mol wt: 635.8521

ACTION – A derivative of the known compound Hoechst 33258 that, like the later, has the ability to bind to DNA. Expected to be useful for transferring nucleic acids into cells, protecting DNA from degradation by endonucleases, and for visual display of nucleic acids by fluorescence microscopy. Another exemplified oligobenzimidazole is:



304929: C44 H61 N7 O2

SOURCE – Aventis Pharma.

REFERENCES

1. Scherman, D. et al. (Aventis Pharma SA) *Oligobenzimidazole derivs. and their use as DNA transfection agents.* FR 2800736, WO 0132630.

SOURCE – Banyu.

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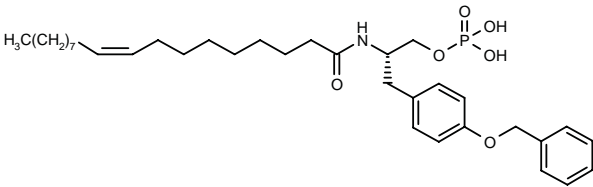
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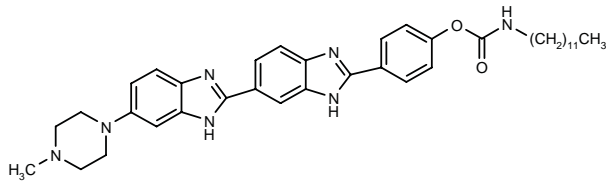
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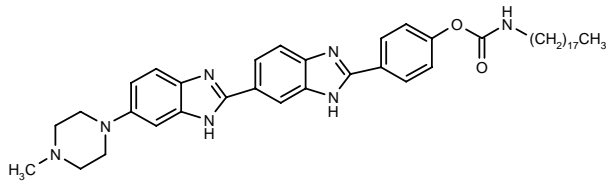
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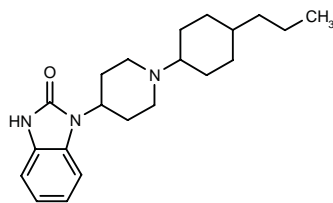
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ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

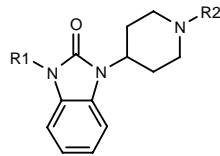
306339

1-[1-(4-Propylcyclohexyl)piperidin-4-yl]-2,3-dihydro-1*H*-benzimidazol-2-one



C21 H31 N3 O; Mol wt: 341.4959

ACTION – Agent with affinity for the opioid receptor-like ORL1 ($K_i = 394$ nM) and mu opioid receptors ($K_i = 19$ nM), and lower affinity for kappa and delta opioid receptors ($K_i = 270$ and $> 10,000$ nM, respectively). Potentially useful for the treatment of acute and chronic pain. Other exemplified 2-oxo-1-piperidinylbenzimidazole are:



Compound	R1	R2	Formula
306340	Ac	4-Pr-cyclohexyl	C ₂₃ H ₃₃ N ₃ O ₂
306341	H	4-Pr-1-cyclohexen-1-yl	C ₂₁ H ₂₉ N ₃ O
306342	H	(CH ₂) ₃ CF ₂ Ph	C ₂₂ H ₂₅ F ₂ N ₃ O
306343	H	4-Ph-PhCH ₂	C ₂₅ H ₂₅ N ₃ O

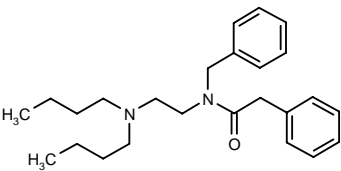
SOURCE – Euroceltique.

REFERENCES

1. Kyle, D. et al. (Euroceltique SA) *Benzimidazole cpds. having nociceptin receptor affinity*. WO 0139775.

306344

N-Benzyl-*N*-[2-(dibutylamino)ethyl]-2-phenylacetamide



C₂₅ H₃₆ N₂ O; Mol wt: 380.5724

ACTION – A representative compound from a series of tertiary amino compounds with affinity for opioid receptors and thus potentially useful for the treatment of acute and chronic pain. The compound exhibited affinity for mu opioid receptors ($K_i = 40$ nM), and lower affinity for kappa and delta opioid receptors ($K_i = 3500$ and $> 10,000$ nM, respectively).

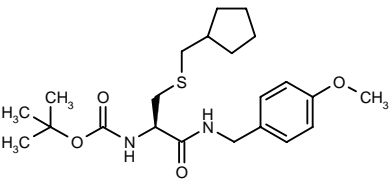
SOURCE – Euroceltique.

REFERENCES

1. Kyle, D. et al. (Euroceltique SA) *Tertiary amino cpds. having opioid receptor affinity*. WO 0139767.

306935

N-[2-(Cyclopentylmethylsulfanyl)-1(*R*)-[*N*-(4-methoxybenzyl)carbamoyl]ethyl]carbamic acid *tert*-butyl ester



C₂₂ H₃₄ N₂ O₄ S; Mol wt: 422.5866

ACTION – Analgesic agent, a selective N-type calcium channel blocker ($IC_{50} = 0.63$ and 3.9 μ M for N- and L-type calcium channels, respectively) proven to block N-type calcium channel currents in an electrophysiological assay in IMR-32 cells (45% at 10 μ M) and to have analgesic effects in the rat formalin test (43% inhibition of paw flinching at 100 mg/kg p.o; 47% inhibition at 3 nmol/rat intrathecally).

SOURCE – Ono.

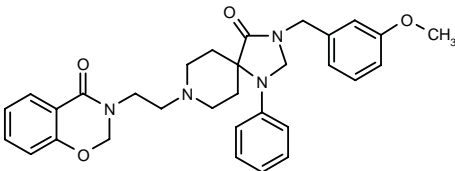
REFERENCES

1. Seko, T. and Kato, M. (Ono Pharmaceutical Co., Ltd.) *Amino acid derivs.* EP 0997147, WO 9902146.

2. Seko, T. et al. *Structure-activity study and analgesic efficacy of amino acid derivatives as N-type calcium channel blockers.* Bioorg Med Chem Lett 2001, 11(16): 2067.

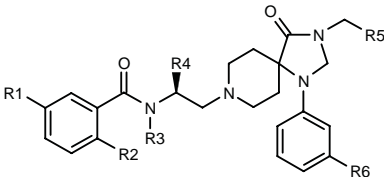
307215

3-[2-[3-(3-Methoxybenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl]ethyl]-3,4-dihydro-2H-1,3-benzoxazin-4-one



C31 H34 N4 O4; Mol wt: 526.6336

ACTION – Delta opioid receptor agonist (K_i = 217 nM against [3 H]-naltrindole binding in rat brain preparations), potentially useful for the treatment or prevention of CNS disorders such as schizophrenia, depression, stroke, epilepsy, Alzheimer’s disease and Parkinson’s disease, as well as peripheral nerve disorders such as pain. Within this series of spiro derivatives, the following compounds are also included:



Compound	R1	R2,R3	R4	R5	R6	Formula
307216	H	-(CH2)2-	H	Ph	H	C ₃₁ H ₃₄ N ₄ O ₂
307217	OMe	-OCH2-	H	cyclopropyl	H	C ₂₈ H ₃₄ N ₄ O ₄
307218	H	-OCH2-	H	Ph	OMe	C ₃₁ H ₃₄ N ₄ O ₄
307219	H	-OCH2-	CH2Ph	cyclopropyl	H	C ₃₄ H ₃₈ N ₄ O ₃
307220	H	-OCH2-	H	cyclohexyl	H	C ₃₀ H ₃₈ N ₄ O ₃
307221	H	-OCH2-	H	3-F-Ph	H	C ₃₀ H ₃₁ FN ₄ O ₃
307222	H	-OCH2-	H	2-Me-Ph	H	C ₃₁ H ₃₄ N ₄ O ₃
307223	H	-OCH2-	H	2-CN-Ph	H	C ₃₁ H ₃₁ N ₅ O ₃
307224	H	-SCH2-	H	Ph	H	C ₃₀ H ₃₂ N ₄ O ₂ S
307225	H	-NHCH2-	H	cyclopropyl	H	C ₂₇ H ₃₃ N ₅ O ₂
307226	H	-N=CH-	H	Ph	H	C ₃₀ H ₃₁ N ₅ O ₂

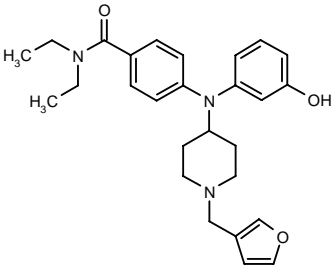
SOURCE – Meiji Seika.

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1. Tsushima, M. et al. (Meiji Seika Kaisha, Ltd.) *Spiro cpds. useful as opioid δ receptor agonist.* WO 0146192.

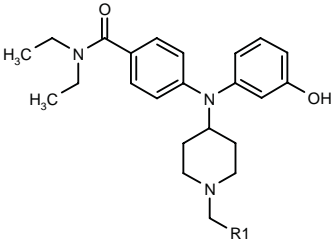
307485

N,N-Diethyl-4-[*N*-[1-(furan-3-ylmethyl)piperidin-4-yl]-*N*-(3-hydroxyphenyl)amino]benzamide



C27 H33 N3 O3; Mol wt: 447.5757

ACTION – Analgesic agent with delta opioid receptor-agonist activity, particularly useful for the treatment of gastrointestinal disorders and spinal injury-related pain. Other exemplified *N,N*-diethylbenzamides are:



Compound	R1	Formula
307486	3-thienyl	C ₂₇ H ₃₃ N ₃ O ₂ S
307487	2-Pyr	C ₂₈ H ₃₄ N ₄ O ₂

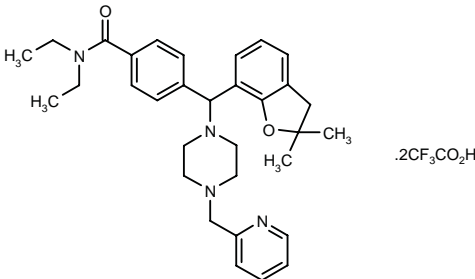
SOURCE – AstraZeneca.

REFERENCES

1. Brown, W. and Walpole, C. (AstraZeneca AB) *Novel cpds.* WO 0146263.

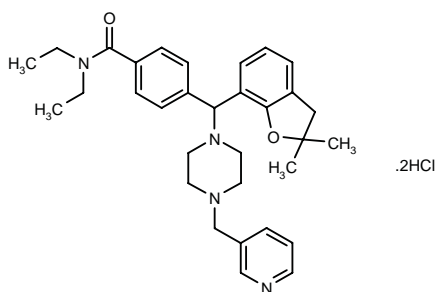
307488

4-[1-(2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-yl)-1-[4-(pyridin-2-ylmethyl)piperazin-1-yl]methyl]-*N,N*-diethylbenzamide bis(trifluoroacetate)



C32 H40 N4 O2 . 2 C2 H F3 O2; Mol wt: 740.7378

ACTION – Analgesic agent with delta opioid receptor-agonist activity, particularly useful for the treatment of gastrointestinal disorders and spinal injury-related pain. Other exemplified *N,N*-diethylbenzamides are:



307489: C₃₂ H₄₀ N₄ O₂ · 2HCl

SOURCE – AstraZeneca.

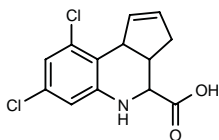
REFERENCES

1. Brown, W. and Walpole, C. (AstraZeneca AB) *Novel cpds.* WO 0146174.

GRT-1539R

308675

7,9-Dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-4-carboxylic acid



C₁₃ H₁₁ Cl₂ N O₂; Mol wt: 284.1409

ACTION – A glycine-site NMDA receptor antagonist with a K_i of 0.3 μ M for the glycine-site NMDA receptor and antinociceptive activity in the formalin test following i.p. administration to rats (21.5 mg/kg). Potentially useful for the treatment of pain and migraine, as well as other NMDA receptor-mediated conditions including urinary incontinence, pruritus, diarrhea, epilepsy, Parkinson's disease, Huntington's disease, glaucoma, osteoporosis, drug and alcohol abuse, stroke, hypoxia, anoxia, anxiety, schizophrenia, Alzheimer's disease, etc.

SOURCE – Grünenthal.

REFERENCES

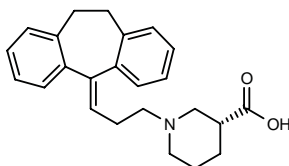
1. Gerlach, M. et al. (Grünenthal GmbH) *Substd. 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivs.* WO 0158875.

REN-1869

236612

1-[3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-idene)propyl]piperidine-3(*R*)-carboxylic acid

NNC-05-1869



C₂₄ H₂₇ N O₂; Mol wt: 361.4823

ACTION – Histamine H₁ receptor antagonist proven to inhibit electrically induced calcitonin gene-related peptide (CGRP) release from rat spinal cord (IC₅₀ = 30 nM) without interfering with Na⁺, Ca²⁺ channels or other receptors. Compound exhibited analgesic effects in several preclinical models including the rat formalin test, the mouse capsaicin paw test and the spinal nerve ligation model of neuropathy in rats. Moreover, it showed antiinflammatory activity in rodents in the carrageenan model of inflammation and the histamine-induced paw edema model. In mice, compound appeared to readily cross the blood–brain barrier, although no sedation or other behavioral disturbances were observed at doses up to 100 mg/kg i.p. In human subjects, oral pharmacokinetics appeared to be independent of age and gender and were slightly reduced by food. In a double-blind, randomized, crossover trial in healthy volunteers, single oral doses (95 mg) significantly reduced histamine-induced wheal, flare and itching, but only slightly reduced capsaicin-induced flare. The compound therefore appears to act at both peripheral and central H₁ receptors.

SOURCES – Novo Nordisk; ReNeuron.

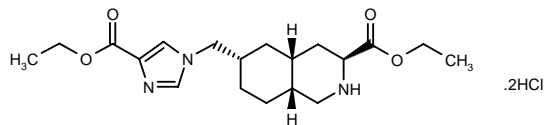
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2. Andersen, T.M. et al. (Novo Nordisk A/S) *Novel formulation.* WO 0037081.
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6. Olsen, U.B. (Novo Nordisk A/S) *Novel method.* JP 1999507947, WO 9722338.
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8. Olsen, U.B. et al. *ReN 1869 is a new tricyclic H₁ receptor antagonist with pain relieving properties.* Inflamm Res 2001, 50(Suppl. 3): Abst 073.
9. Suzuki, R. et al. *Electrophysiological study of the effect of ReN-1869 on the responses of rat dorsal horn neurones following persistent pain states.* Inflamm Res 2001, 50(Suppl. 3): Abst 07/03.
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ANTIMIGRAINE DRUGS

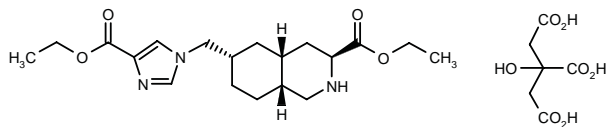
307483

(3*S*,4*aR*,6*S*,8*aR*)-6-[4-(Ethoxycarbonyl)-1*H*-imidazol-1-ylmethyl]perhydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride



C19 H29 N3 O4 . 2HCl; Mol wt: 436.3769

ACTION – Ionotropic glutamate receptor antagonist, particularly selective for the kainate GluR5 subtype, potentially useful for the treatment of migraine. Another specifically claimed salt is:



307484: C19 H29 N3 O4 . C6 H8 O7

SOURCE – Lilly.

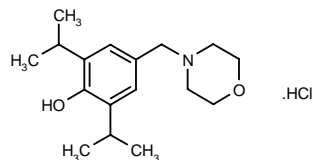
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1. Bell, M.G. et al. (Eli Lilly and Company) *Selective iGLUR5 receptor antagonists*. WO 0146173.

ANESTHETIC DRUGS

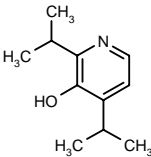
307755^{1,2}

2,6-Diisopropyl-4-(4-morpholinylmethyl)phenol hydrochloride



C17 H27 N O2 . HCl; Mol wt: 313.8662

ACTION – Water-soluble propofol analogue with intravenous anesthetic activity in mice (ED₅₀ = 32 μmol/kg for hypnosis induction); unlike the parent compound it showed no affinity for GABA_A receptors. Electroencephalographic studies in rats demonstrated that the anesthetic profile of compound was similar to propofol, with slightly lower potency and a slower onset. Another related compound is:



307756¹: C11 H17 N O

SOURCE – Organon.

REFERENCES

1. Buchanan, K. et al. *Novel water-soluble propofol analogs with intravenous anaesthetic activities*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 226.

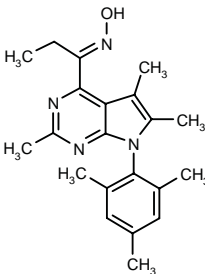
2. Cooke, A. et al. *Water-soluble propofol analogues with intravenous anaesthetic activity*. Bioorg Med Chem Lett 2001, 11(7): 927.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

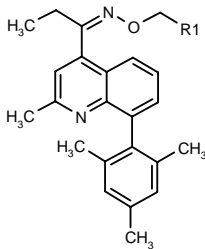
305574

(*E*)-1-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]propan-1-one oxime



C21 H26 N4 O; Mol wt: 350.4634

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of a wide range of disorders such as anxiety, depression, phobias, stress-induced disorders, schizophrenia, headache, cancer, irritable bowel syndrome, inflammatory disorders, neurodegenerative diseases, gastrointestinal disorders, eating disorders, drug and alcohol withdrawal symptoms, infertility and stroke. Other specifically claimed substituted heterocyclic compounds include the following:

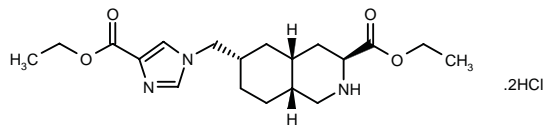


Compound	R1	Formula
305575	H	C ₂₃ H ₂₆ N ₂ O
305577	i-Pr	C ₂₆ H ₃₂ N ₂ O

ANTIMIGRAINE DRUGS

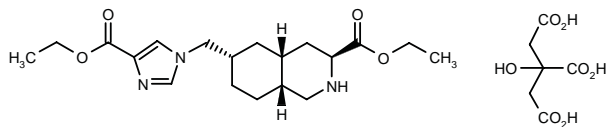
307483

(3*S*,4*aR*,6*S*,8*aR*)-6-[4-(Ethoxycarbonyl)-1*H*-imidazol-1-ylmethyl]perhydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride



C19 H29 N3 O4 . 2HCl; Mol wt: 436.3769

ACTION – Ionotropic glutamate receptor antagonist, particularly selective for the kainate GluR5 subtype, potentially useful for the treatment of migraine. Another specifically claimed salt is:



307484: C19 H29 N3 O4 . C6 H8 O7

SOURCE – Lilly.

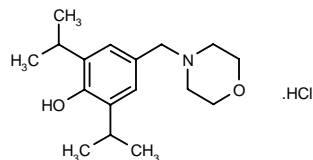
REFERENCES

1. Bell, M.G. et al. (Eli Lilly and Company) *Selective iGLUR5 receptor antagonists*. WO 0146173.

ANESTHETIC DRUGS

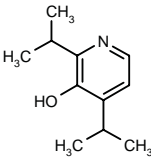
307755^{1,2}

2,6-Diisopropyl-4-(4-morpholinylmethyl)phenol hydrochloride



C17 H27 N O2 . HCl; Mol wt: 313.8662

ACTION – Water-soluble propofol analogue with intravenous anesthetic activity in mice (ED₅₀ = 32 μmol/kg for hypnosis induction); unlike the parent compound it showed no affinity for GABA_A receptors. Electroencephalographic studies in rats demonstrated that the anesthetic profile of compound was similar to propofol, with slightly lower potency and a slower onset. Another related compound is:



307756¹: C11 H17 N O

SOURCE – Organon.

REFERENCES

1. Buchanan, K. et al. *Novel water-soluble propofol analogs with intravenous anaesthetic activities*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 226.

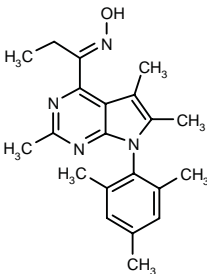
2. Cooke, A. et al. *Water-soluble propofol analogues with intravenous anaesthetic activity*. Bioorg Med Chem Lett 2001, 11(7): 927.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

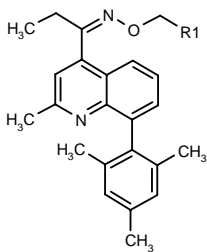
305574

(*E*)-1-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]propan-1-one oxime

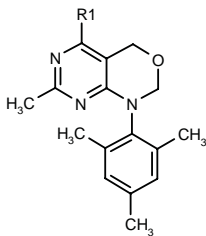


C21 H26 N4 O; Mol wt: 350.4634

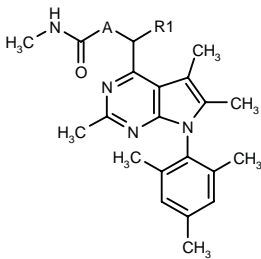
ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of a wide range of disorders such as anxiety, depression, phobias, stress-induced disorders, schizophrenia, headache, cancer, irritable bowel syndrome, inflammatory disorders, neurodegenerative diseases, gastrointestinal disorders, eating disorders, drug and alcohol withdrawal symptoms, infertility and stroke. Other specifically claimed substituted heterocyclic compounds include the following:



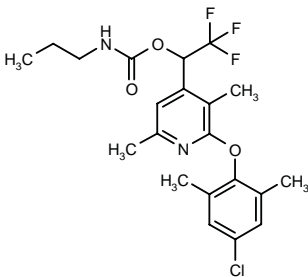
Compound	R1	Formula
305575	H	C ₂₃ H ₂₆ N ₂ O
305577	i-Pr	C ₂₆ H ₃₂ N ₂ O



Compound	R1	Formula
305576	(E)-C(=NOH)Et	C ₁₉ H ₂₄ N ₄ O ₂
305580	CH(CF ₃)OCONHMe	C ₂₀ H ₂₃ F ₃ N ₄ O ₃



Compound	R1	A	Formula
305579	Et	O	C ₂₃ H ₃₀ N ₄ O ₂
305581	2-thiazolyl	NH	C ₂₄ H ₂₈ N ₆ OS



305578: C₂₁ H₂₄ Cl F₃ N₂ O₃

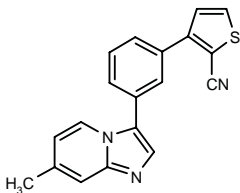
SOURCE – Pfizer.

REFERENCES

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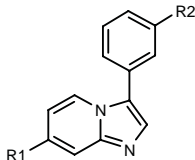
305640

3-[3-(7-Methylimidazo[1,2-*a*]pyridin-3-yl)phenyl]thio-
phene-2-carbonitrile



C₁₉ H₁₃ N₃ S; Mol wt: 315.3987

ACTION – Agent with high affinity for the α 2 and/or α 3 subunit of the human GABA_A receptor (K_i = 100 nM or less against [³H]-flumazenil binding to the α 2 and/or α 3 subunit of the human GABA_A receptor stably expressed in Ltk-cells), with potential for the treatment of CNS disorders, particularly anxiety and convulsions. Other specifically claimed compounds from this series of 3-phenylimidazo[1,2-*a*]pyridine derivatives include the following:



Compound	R1	R2	Formula
305641	Me	2-(CO ₂ Me)-3-thienyl	C ₂₀ H ₁₆ N ₂ O ₂ S
305642	Me	4-Pyr	C ₁₉ H ₁₅ N ₃
305643	CH=NOH	3-Pyr	C ₁₉ H ₁₄ N ₄ O
305644	OMe	3-Pyr	C ₁₉ H ₁₅ N ₃ O
305645	Me	2-CN-Ph	C ₂₁ H ₁₅ N ₃
305646	CH=NOH	2-CN-3-thienyl	C ₁₉ H ₁₂ N ₄ OS
305652	CH=NOCH ₂ -CH ₂ N(Me) ₂	2-CN-3-thienyl	C ₂₃ H ₂₁ N ₅ OS
305653	CH ₂ F	2-CN-Ph	C ₂₁ H ₁₄ FN ₃

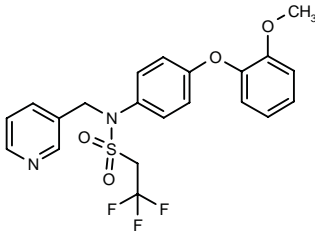
SOURCE – Merck Sharp & Dohme.

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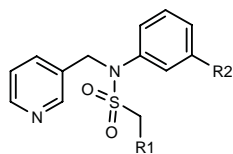
308166

2,2,2-Trifluoro-*N*-[4-(2-methoxyphenoxy)phenyl]-*N*-(
pyridin-3-ylmethyl)ethanesulfonamide



C₂₁ H₁₉ F₃ N₂ O₄ S; Mol wt: 452.4511

ACTION – Metabotropic glutamate receptor (mglu₂ and/or mglu₃) potentiator, as demonstrated *in vitro* by its ability to potentiate the mglu₂ agonist-induced increase in intra-cellular calcium. *In vivo*, it inhibited by nearly 50% electrical stimulation-induced dural protein extravasation following i.v. administration to rats (100 ng/kg). In addition, it was active in a fear-potentiated startle paradigm when given i.p. to rats. Potentially useful for the treatment of neurological and psychopharmacological disorders, particularly anxiety, migraine, schizophrenia and epilepsy. Other exemplified compounds are:



Compound	R1	R2	Formula
308167	CF3	2-MeO-PhO	C ₂₁ H ₁₉ F ₃ N ₂ O ₄ S
308168	CF3	2-(PhCH2O)-PhO	C ₂₇ H ₂₃ F ₃ N ₂ O ₄ S
308169	Me	4-CN-Ph	C ₂₁ H ₁₉ N ₃ O ₂ S

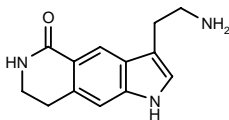
SOURCE – Lilly.

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1. Coleman, D.S. et al. (Eli Lilly and Company) *Potentiators of glutamate receptors*. WO 0156990.

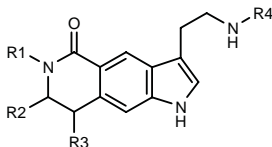
308365

3-(2-Aminoethyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*g*]isoquinolin-5-one



C13 H15 N3 O; Mol wt: 229.2815

ACTION – 5-HT₇ receptor modulator with a K_i of 14 nM against human recombinant 5-HT₇ receptors. Potentially useful for the treatment of anxiety, depression and other CNS disorders including schizophrenia, sleep disorders, migraine, drug and alcohol withdrawal and sexual dysfunction, as well as hypotension, renal disorders, septic shock, diarrhea and spastic colon. Other specifically claimed pyrrolo[2,3-*g*]isoquinoline derivatives are:



Compound	R1	R2	R3	R4	Formula
308366	CH2Ph	H	H	H	C ₂₀ H ₂₁ N ₃ O
308368	CH2Ph	bond		H	C ₂₀ H ₁₉ N ₃ O
308369	H	H	H	CH2Ph	C ₂₀ H ₂₁ N ₃ O

SOURCE – American Home Products.

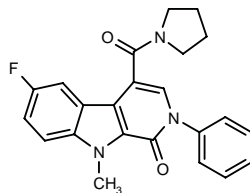
REFERENCES

1. Kelly, M.G. and Kang, Y.H. (American Home Products Corp.) *Pyrrolo-isoquinoline and tetrahydropyrrolo-isoquinoline derivs. and their use as mediators of the 5-HT₇ receptor*. WO 0157039.

SL-65.1498*

290452

6-Fluoro-9-methyl-2-phenyl-4-(pyrrolidin-1-ylcarbonyl)-2,9-dihydro-1*H*-pyrido[3,4-*b*]indole-1-one



C23 H20 F N3 O2; Mol wt: 389.4280

ACTION – High-affinity ligand for the α1 and α2 subunits of the GABA_A receptor (K_i = 6.8 and 12.3 nM, respectively), with lower affinity for the α5 subunit (K_i = 117 nM). Using recombinant rat receptors, compound exhibited respective K_i values for α1β2γ2, α2β2γ2, α3β2γ2 and α5β3γ2 receptor subtypes of 17, 73, 80.3 and 215 nM. It acts as a full agonist at α2 and α3 GABA_A subunits and as a partial agonist at α1 and α5 subunits, as demonstrated in electrophysiological studies using recombinant rat GABA_A receptors. *In vivo*, compound showed anti-convulsant activity in mice and was more active against seizures induced by pentylenetetrazol than those induced by maximal electroshock. This anticonvulsant profile is consistent with partial agonist activity or preferential affinity for the α1 subunit of GABA_A receptors. Anxiolytic-like activity was seen in several experimental paradigms in rats and mice including the elevated plus-maze test in rats, the light/dark test in mice and the defense test in mice, with minimum effective doses of about 1-10 mg/kg i.p. or p.o. Side effects of muscle weakness, ataxia or sedation were observed only at doses of 30 mg/kg or greater. No tolerance was seen to either the anti-convulsant or the anxiolytic effects of the drug after repeated dosing. Compared to diazepam, compound exhibited similar anxiolytic activity and reduced motor and other side effects. Potentially useful as an anxiolytic agent.

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Evanno, Y. et al. (Sanofi-Synthélabo) *1*H*-Pyrido[3,4-*b*]indole-4-carboxamide derivs., preparation and application thereof in therapeutics*. FR 2754262, JP 2001508403, US 6075021, WO 9815552.

2. Griebel, G. et al. *SL651498: A new anxiolytic with functional selectivity for GABA_{A2A} and GABA_{A3A} receptor subtypes*. Soc Neurosci Abst 2000, 26(Part 2): Abst 684.2.

3. Griebel, G. et al. *SL651498: An anxiolytic compound with functional selectivity for α₂- and α₃-containing γ-aminobutyric acidA (GABA_A) receptors*. J Pharmacol Exp Ther 2001, 298(2): 753.

4. Scatton, B. et al. *Selectivity for GABA_A receptor alpha subunits as a strategy for developing hypnosedative and anxiolytic agents*. Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst S.41.3.

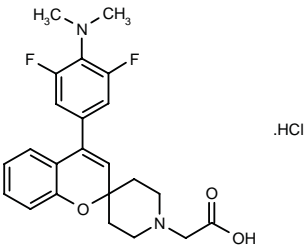
5. *Sanofi-Synthelabo presents overhauled R&D portfolio to financial analysis*. DailyDrugNews.com (Daily Essentials) 2000, March 21.

*Identified compound **290452** (see **290444**) Drug Data Rep 2000, 022(09): 0773.

ANTIPSYCHOTIC DRUGS

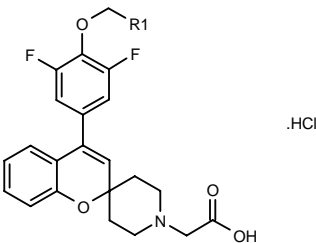
305501

2-[4-[4-(Dimethylamino)-3,5-difluorophenyl]spiro[2*H*-1-benzopyran-2,4'-piperidin]-1'-yl]acetic acid hydrochloride



C23 H24 F2 N2 O3 . HCl ; Mol wt: 450.9105

ACTION – Selective glycine transporter GlyT-1 inhibitor (pIC₅₀ = 6.6 for inhibition of glycine uptake in CHO cells transfected with the hGlyT-1b transporter), potentially useful for the treatment or prevention of CNS disorders, particularly schizophrenia, depression, dementia, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease and other neurodegenerative diseases, as well as muscle hyperactivity associated with spasticity, myoclonus and epilepsy. Other exemplified compounds from this series of spiro[2*H*-1-benzopyran-2,4'-piperidine] derivatives include the following:



Compound	R1	Formula
305502	vinyl	C ₂₄ H ₂₃ F ₂ NO ₄ .HCl
305503	ethynyl	C ₂₄ H ₂₁ F ₂ NO ₄ .HCl
305504	CF3	C ₂₃ H ₂₀ F ₅ NO ₄ .HCl

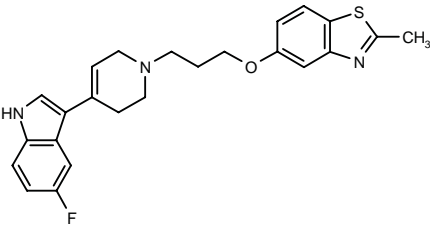
SOURCE – Akzo Nobel.

REFERENCES

1. Gibson, S.G. and Miller, D.J. (Akzo Nobel N.V.) *Spiro(2*H*-1-benzopyran-2,4'-piperidine) derivatives as glycine transport inhibitors*. WO 0136423.

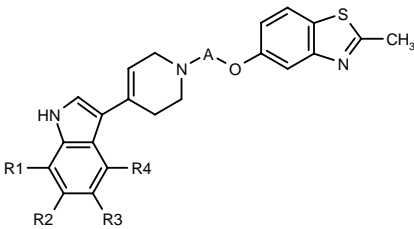
307126

5-[3-[4-(5-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]propoxy]-2-methylbenzothiazole

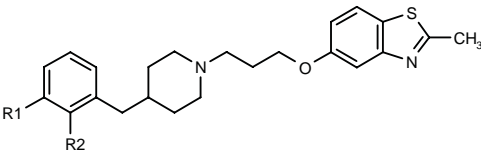


C24 H24 F N3 O S; Mol wt: 421.5376

ACTION – Antipsychotic agent that acts as both a 5-HT reuptake inhibitor and a dopamine D2L receptor antagonist. Also potentially useful as an antidepressant. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
307127	H	H	CN	H	-(CH2)4-	C ₂₆ H ₂₆ N ₄ OS
307128	H	H	H	F	-(CH2)5-	C ₂₆ H ₂₈ FN ₃ OS
307129	F	H	H	H	-(CH2)5-	C ₂₆ H ₂₈ FN ₃ OS
307130	H	Cl	H	H	-(CH2)5-	C ₂₆ H ₂₈ ClN ₃ OS
307131	Br	H	H	H	-(CH2)4O(CH2)4-	C ₂₉ H ₃₄ BrN ₃ O ₂ S



Compound	R1	R2	Formula
307132	-OCH2O-		C ₂₄ H ₂₈ N ₂ O ₃ S
307133	OMe	H	C ₂₄ H ₃₀ N ₂ O ₂ S

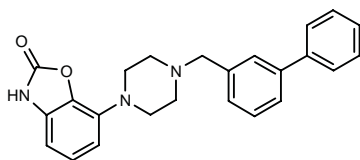
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Mattson, R.J. et al. (Bristol-Myers Squibb Co.) *Antipsychotic heterocycle cpds*. WO 0143740.

308000

7-[4-(Biphenyl-3-ylmethyl)piperazin-1-yl]benzoxazol-2(3H)-one



C24 H23 N3 O2; Mol wt: 385.4647

ACTION – Potential antipsychotic agent with nanomolar affinity for dopamine D2 and 5-HT_{1A} receptors (K_i = 2.2 and 9.3 nM, respectively). Compound exhibited favorable pharmacokinetic properties and showed efficacy in *in vivo* models relevant for antipsychotic activity including apomorphine-induced climbing behavior in mice (ED_{50} = 0.1 mg/kg p.o.), a conditioned avoidance response in rats (ED_{50} = 0.8 mg/kg p.o.) and the rat lower lip retraction model (ED_{50} = 10 mg/kg p.o.).

SOURCE – Solvay.

REFERENCES

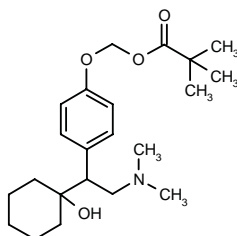
1. Feenstra, R.W. et al. (Duphar International Research BV) *Piperazine and piperidine cpds.* JP 2000507949, US 6225312, WO 9736893.

2. Feenstra, R.W. et al. *New 1-aryl-4-(biaryl)methylene)piperazines as potential atypical antipsychotics sharing dopamine D₂-receptor and serotonin 5-HT_{1A}-receptor affinities.* Bioorg Med Chem Lett 2001, 11(17): 2345.

TREATMENT OF MOOD DISORDERS

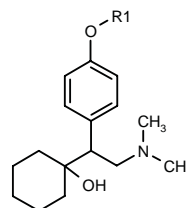
305592

2,2-Dimethylpropionic acid [4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy]methyl ester



C22 H35 N O4; Mol wt: 377.5215

ACTION – A representative compound from a series of *O*- α -acyloxyalkyl ethers of *O*-desmethyl venlafaxine that exhibit the same biological activities as venlafaxine. Potentially useful for the treatment of CNS disorders, particularly depression, anxiety, panic disorder, post-traumatic stress disorder, attention deficit disorder, schizophrenia, drug and alcohol addiction, premenstrual dysphoric disorder, autism, anorexia nervosa, bulimia nervosa, vasomotor flushing, chronic fatigue syndrome, urinary incontinence, pain and sexual dysfunction, and for enhancing cognition. Other specifically claimed compounds are:



Compound	R1	Formula
305593	CH(Me)OCOEt	C ₂₁ H ₃₃ NO ₄
305594	1-oxo-1,3-dihydro-3-isobenzofuryl	C ₂₄ H ₂₉ NO ₄

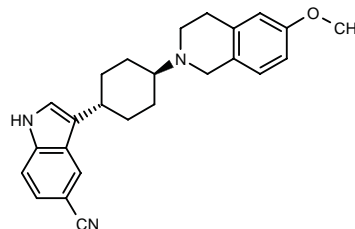
SOURCE – American Home Products.

REFERENCES

1. Yardley, J.P. et al. (American Home Products Corp.) *Ethers of O-desmethyl venlafaxine.* WO 0138293.

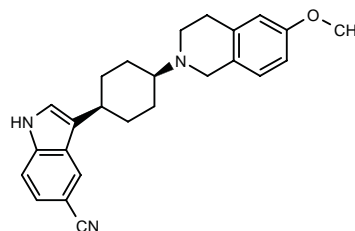
307816

trans-3-[4-[6-Methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]-cyclohexyl]-1H-indole-5-carbonitrile



C25 H27 N3 O; Mol wt: 385.5083

ACTION – Potent 5-HT reuptake inhibitor (K_i = 8 nM) with moderate affinity for 5-HT_{1A} receptors (K_i = 300 nM) and selectivity over α_1 -adrenoceptors. Potentially useful as an antidepressant. Another indolylcyclohexylamine is:



287506: C25 H27 N3 O

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Mewshaw, R.E. and Meagher, K.L. (American Home Products Corp.) *Tetrahydro-isoquinolinyl-indole derivs. for the treatment of depression.* WO 0064886.

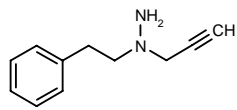
2. Meagher, K.L. et al. *Studies towards the next generation of antidepressants. Part 1: Indolylcyclohexylamines as potent serotonin reuptake inhibitors.* Bioorg Med Chem Lett 2001, 11(14): 1885.

3. Mewshaw, R.E. et al. *Indolylcyclohexylamines as potent serotonin reuptake inhibitors.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 108.

CVT-P040^{1,2}

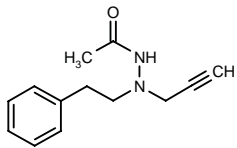
308651

1-(2-Phenylethyl)-1-(2-propynyl)hydrazine



C11 H14 N2; Mol wt: 174.2456

ACTION – Monoamine oxidase (MAO) inhibitor (IC₅₀ = 2.04 and 0.0765 μM against MAO-A and MAO-B sub-types, respectively) able to strongly inhibit brain and liver MAO-A and MAO-B in rats after i.p. or p.o. administration, with a comparable effect to phenelzine. However, unlike phenelzine, CVT-P040 did not elevate GABA concentrations in rat brain. CVT-P040 (10 mg/kg i.p.) was also found to reduce DSP-4-induced noradrenaline depletion in the hippocampus of mice. Potentially useful as an antidepressant with prophylactic properties against neurodegenerative diseases. Another related compound is:



CVT-P041² [308663]: C13 H16 N2 O

SOURCE – CV Technologies.

REFERENCES

1. Ling, L. et al. *Synthesis of N-propargylphenelzine and analogues as neuroprotective agents*. Bioorg Med Chem Lett 2001, 11(20): 2715.

2. Sloley, B.D. et al. *Monoamine oxidase inhibition and neuroprotection by N-1-propargylphenelzine*. Drug Dev Res 2001, 53(1): 15.

NEUROLOGIC DRUGS

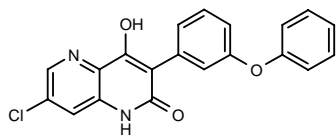
ANTIEPILEPTIC DRUGS

ACEA-762

267988

7-Chloro-4-hydroxy-3-(3-phenoxyphenyl)-1,5-naphthyridin-2(1*H*)-one

ACEA-0762



C20 H13 Cl N2 O3; Mol wt: 364.7867

ACTION – Anticonvulsant, an NMDA receptor glycine site antagonist with an IC₅₀ value of 110 nM in a binding assay and a K_b of 11 nM in an electrophysiological assay. *In vivo*, compound protected mice against seizures induced by maximum electroshock with an ED₅₀ of 2.3 mg/kg i.p.

SOURCE – CoCensys (Purdue Pharma).

REFERENCES

1. Keana, J.F.W. et al. (Oregon Health Sciences University) *Aza and aza (N-oxy) analogs of glycine/NMDA receptor antagonists*. EP 0805809, US 5801183, WO 9622990.

2. Lan, N.C. (CoCensys, Inc.) *Use of GABA and NMDA receptor ligands for the treatment of migraine headache*. WO 9805337.

3. Luffy, K. et al. *ACEA-1328, an NMDA receptor antagonist, increases the potency of morphine and U50,488H in the tail flick test in mice*. Pharmacol Res 1998, 38(6): 453.

4. Luffy, K. et al. *Antinociceptive effects of NMDA and non-NMDA receptor antagonists in the tail flick test in mice*. Pain 1997, 70(1): 31.

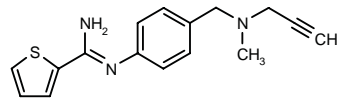
5. Zhou, Z.-L. et al. *Synthesis and SAR of 5-, 6-, 7- and 8-aza-3-aryl-4-hydroxyquinolin-2(1H)-ones as NMDA/glycine site antagonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 113.

6. Zhou, Z.-L. et al. *Synthesis and SAR of 5-, 6-, 7- and 8-aza analogues of 3-aryl-4-hydroxyquinolin-2(1H)-ones as NMDA/glycine site antagonists*. Bioorg Med Chem 2001, 9(8): 2061.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

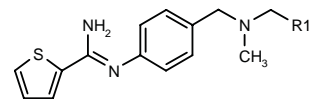
305467

N'-[4-[N-Methyl-N-(2-propynyl)aminomethyl]phenyl]thiophene-2-carboxamide



C16 H17 N3 S; Mol wt: 283.3973

ACTION – A representative compound from a series of amidine derivatives that inhibit nitric oxide synthase (NOS) and/or monoamine oxidase (MAO), particularly MAO-B, and are potentially useful for the treatment of a broad range of disorders, particularly Parkinson's disease, senile dementia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, schizophrenia, depression and psychoses. Other specifically claimed compounds are:

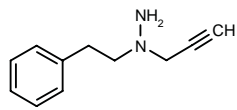


Compound	R1	Formula
305470	CN	C ₁₅ H ₁₆ N ₄ S
305471	Et	C ₁₆ H ₂₁ N ₃ S
305473	CH2CN	C ₁₆ H ₁₈ N ₄ S
305474	ethynyl-CH2CH2	C ₁₈ H ₂₁ N ₃ S

CVT-P040^{1,2}

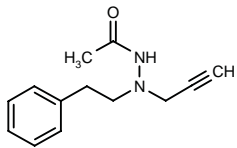
308651

1-(2-Phenylethyl)-1-(2-propynyl)hydrazine



C11 H14 N2; Mol wt: 174.2456

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CVT-P041² [308663]: C13 H16 N2 O

SOURCE – CV Technologies.

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NEUROLOGIC DRUGS

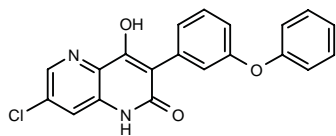
ANTIEPILEPTIC DRUGS

ACEA-762

267988

7-Chloro-4-hydroxy-3-(3-phenoxyphenyl)-1,5-naphthyridin-2(1*H*)-one

ACEA-0762



C20 H13 Cl N2 O3; Mol wt: 364.7867

ACTION – Anticonvulsant, an NMDA receptor glycine site antagonist with an IC₅₀ value of 110 nM in a binding assay and a K_b of 11 nM in an electrophysiological assay. *In vivo*, compound protected mice against seizures induced by maximum electroshock with an ED₅₀ of 2.3 mg/kg i.p.

SOURCE – CoCensys (Purdue Pharma).

REFERENCES

1. Keana, J.F.W. et al. (Oregon Health Sciences University) *Aza and aza (N-oxy) analogs of glycine/NMDA receptor antagonists*. EP 0805809, US 5801183, WO 9622990.

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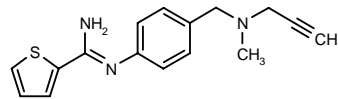
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

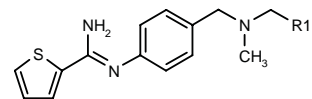
305467

N'-[4-[N-Methyl-N-(2-propynyl)aminomethyl]phenyl]thiophene-2-carboxamide



C16 H17 N3 S; Mol wt: 283.3973

ACTION – A representative compound from a series of amidine derivatives that inhibit nitric oxide synthase (NOS) and/or monoamine oxidase (MAO), particularly MAO-B, and are potentially useful for the treatment of a broad range of disorders, particularly Parkinson's disease, senile dementia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, schizophrenia, depression and psychoses. Other specifically claimed compounds are:



Compound	R1	Formula
305470	CN	C ₁₅ H ₁₆ N ₄ S
305471	Et	C ₁₆ H ₂₁ N ₃ S
305473	CH2CN	C ₁₆ H ₁₈ N ₄ S
305474	ethynyl-CH2CH2	C ₁₈ H ₂₁ N ₃ S

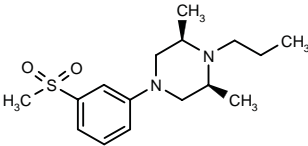
SOURCE – SCRAS.

REFERENCES

1. Chabrier de Lassaulniere, P.-E. and Harnett, J. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel amidine derivs., preparation and use thereof as medicines*. FR 2801053, WO 0136407.

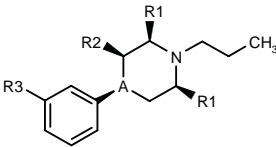
307474

cis-2,6-Dimethyl-4-[3-(methylsulfonyl)phenyl]-1-propylpiperazine



C16 H26 N2 O2 S; Mol wt: 310.4594

ACTION – Dopamine neurotransmission modulator that acts preferentially on dopaminergic systems in the brain, exhibiting effects characteristic of dopamine receptor antagonists, but showing no inhibitory effects on spontaneous locomotion and even mildly stimulating behavioral activity. When tested in rats, compound was shown to increase 3,4-dihydroxy-phenylacetic acid in striatum of rats from 1247 ± 65 ng/g tissue in controls to 3140 ± 169 ng/g tissue at 100 µmol/kg s.c. It was further shown to produce an increase in motor activity (27 ± 11 cm/30 min in controls vs. 253 ± 73 cm/30 min at 100 µmol/kg s.c.), as well as to significantly reduce *d*-amphetamine-induced hyperactivity (21,140 ± 4656 cm/60 min in controls to 2492 ± 530 cm/60 min at 100 µmol/kg s.c.). Potentially useful for the treatment of a broad range of CNS disorders including movement disorders (e.g., Parkinson's disease, dyskinesias and Tourette's disease), psychoses (e.g., schizophrenia), mood and anxiety disorders, attention deficit disorders, autism, cognitive dysfunctions, sleep disorders, sexual disorders, eating disorders and pain. Other compounds from this series of substituted 4-(phenyl-*N*-alkyl)piperazine and 4-(phenyl-*N*-alkyl)piperidine derivatives include the following:



Compound	R1	R2	R3	A	Formula
307476	Me	H	CF3	N	C ₁₆ H ₂₃ F ₃ N ₂
307478	H	Me	SO2Me	CH	C ₁₆ H ₂₅ NO ₂ S

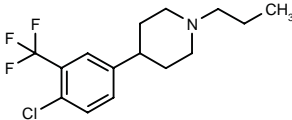
SOURCE – Carlsson Research.

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1. Sonesson, C. et al. (Carlsson Research AB) *New modulators of dopamine neurotransmission*. WO 0146144, WO 0146145.

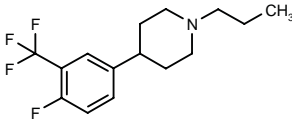
307480

4-[4-Chloro-3-(trifluoromethyl)phenyl]-1-propylpiperidine



C15 H19 Cl F3 N; Mol wt: 305.7691

ACTION – Dopamine neurotransmission modulator that acts preferentially on dopaminergic systems in the brain, exhibiting effects characteristic of dopamine receptor antagonists, but showing only limited inhibitory effects on spontaneous locomotion. When tested in rats, compound was shown to increase 3,4-dihydroxyphenylacetic acid in striatum of rats from 1089 ± 102 ng/g tissue in controls to 1680 ± 136 ng/g tissue at 50 µmol/kg s.c. It was further shown to be devoid of significant inhibition of spontaneous behavior (1287 ± 272 cm/30 min for controls vs. 944 ± 114 cm/30 min at 50 mcmol/kg s.c.) and to have no significant effect on the locomotor activity of habituated rats (1381 ± 877 cm/60 min in controls vs. 1300 ± 761 cm/60 min at 50 µmol/kg s.c.). On the other hand, it significantly reduced *d*-amphetamine-induced hyperactivity (8376 ± 2188 cm/30 min in controls to 3399 ± 1247 cm/30 min at 50 µmol/kg s.c.). Oral bioavailability in rats was 55%. Potentially useful for the treatment of a broad range of CNS disorders including movement disorders (e.g., Parkinson's disease, dyski-nesias and Tourette's disease), psychoses (e.g., schizo-phrenia), mood and anxiety disorders, attention deficit disorders, autism, cognitive dysfunctions, sleep disorders, sexual disorders, eating disorders and pain. Another compound from this series of substituted 4-(phenyl-*N*-alkyl)piperazine and 4-(phenyl-*N*-alkyl)piperidine derivatives is:



307482: C15 H19 F4 N

SOURCE – Carlsson Research.

REFERENCES

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TREATMENT OF IMMUNOLOGIC
NEUROMUSCULAR DISORDERS

MBP(82-98)

306794

L-Aspartyl-L-glutamyl-L-asparaginyl-L-prolyl-L-valyl-L-valyl-L-histidyl-L-phenylalanyl-L-phenylalanyl-L-lysyl-L-asparaginyl-L-isoleucyl-L-valyl-L-threonyl-L-prolyl-L-arginyl-L-threonine

MBP-8298
spMBP(82-98)

C92 H141 N25 O26; Mol wt: 2013.2750

ACTION – Synthetic myelin basic protein (MBP) peptide that binds and neutralizes free autoantibodies to MBP (anti-MBP), currently in phase II clinical trials for the treatment of multiple sclerosis.

SOURCES – University of Alberta, Edmonton, AB (CA); BioMS Medical.

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4. Weiner, H.L. et al. (AutoImmune Inc.) *Suppression of T-cell proliferation using peptide fragments of myelin basic protein*. WO 9321222.

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6. Warren, K.G. and Catz, I. *The effect of intrathecal MBP synthetic peptides containing epitope P85 VVHFFKNIVTP96 on free anti-MBP levels in acute relapsing multiple sclerosis*. J Neurol Sci 1997, 148(1): 67.

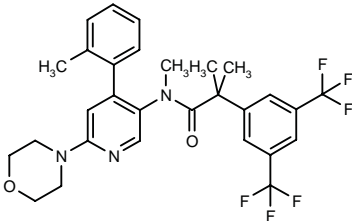
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8. *Synthetic peptide-based treatment for MS completes phase II trial in Canada*. DailyDrugNews.com (Daily Essentials) 2001, Sept 19.

TREATMENT OF NAUSEA AND
VOMITING

305573

2-[3,5-Bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-morpholinyl)pyridin-3-yl]propionamide



C29 H29 F6 N3 O2; Mol wt: 565.5551

ACTION – Potent tachykinin NK₁ receptor antagonist, as demonstrated in binding assays by a pK_i value of 9.0 in CHO cells expressing the human NK₁ receptor, showing selectivity of over 2 orders of magnitude for NK₁ compared to NK₂ and NK₃ receptors. In functional assays, it inhibited substance P-induced calcium influx in CHO cells expressing the human NK₁ receptor with a pA₂ value of 8.9. *In vivo*, it was shown to antagonize foot-tapping behavior induced by i.c.v. injections of an NK₁ receptor agonist in gerbils with an ID₅₀ value of 0.2 mg/kg p.o. and a long duration of action. In addition, it was effective against apomorphine-induced emesis in ferrets (ED₅₀ = 0.1 mg/kg p.o.) and exhibited an ED₅₀ value of 0.2 mg/kg p.o. in a model of motion sickness in suncus murinus. When tested in pharmacokinetic studies in rats and dogs, it exhibited half-lives of 23 and 40 h, respectively, and oral bioavailabilities of 50 and 30-40%, respectively. Claimed for the treatment of NK₁-mediated disorders, particularly emesis, depression and anxiety.

SOURCE – Roche.

REFERENCES

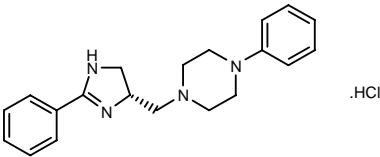
1. Ballard, T.M. et al. (F. Hoffmann-La Roche AG) *2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide*. EP 1103545, JP 2001151754.

TREATMENT OF ATTENTION DEFICIT
HYPERACTIVITY DISORDER

FAUC-179

308577

1-Phenyl-4-[2-phenyl-4,5-dihydro-1H-imidazol-4(R)-ylmethyl]piperazine hydrochloride



C20 H24 N4 . HCl; Mol wt: 356.8985

ACTION – High-affinity dopamine D4 receptor ligand (K_i = 0.95 and 51 nM at high- and low-affinity binding sites, respectively) with excellent selectivity over dopamine D1, D2long, D2short and D3 receptors (K_i = 7,100-12,000 nM). Compound showed partial agonist activity in a mitogenesis assay in CHO cells, with an EC_{50} of 31 nM and an intrinsic activity of 42%. Potentially useful for the treatment of psychotic disorders and attention deficit hyperactivity disorder (ADHD).

SOURCE – Friedrich-Alexander-Universität, Erlangen (DE).

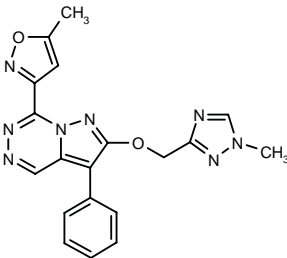
REFERENCES

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TREATMENT OF COGNITION DISORDERS

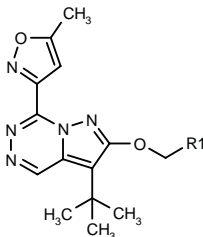
305596

7-(5-Methylisoxazol-3-yl)-2-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenylpyrazolo[1,5-*d*][1,2,4]triazine



C19 H16 N8 O2; Mol wt: 388.3894

ACTION – Agent for enhancing cognition, particularly for the treatment of Alzheimer's disease, with selective affinity for human GABA_A $\alpha 5$ receptors. It exhibits a reduced liability for proconvulsant side effects. Other specifically claimed compounds from this series of pyrazolo[1,5-*d*]-[1,2,4]triazines are:



Compound	R1	Formula
305599	1-Me-1,2,4-triazol-3-yl	C ₁₇ H ₂₀ N ₈ O ₂
305600	1-Me-1,2,4-triazol-5-yl	C ₁₇ H ₂₀ N ₈ O ₂
305602	2-Pyr	C ₁₉ H ₂₀ N ₈ O ₂
305603	3-Pyr	C ₁₉ H ₂₀ N ₈ O ₂

SOURCE – Merck Sharp & Dohme.

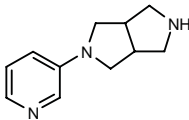
REFERENCES

1. Bryant, H.J. et al. (Merck Sharp & Dohme Ltd.) *Pyrazolo[1,5-*d*][1,2,4]triazines for enhancing cognition*. WO 0138331.

307134

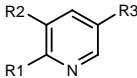
2-(3-Pyridyl)perhydropyrrolo[3,4-*c*]pyrrole

3-(3-Pyridyl)-3,7-diazabicyclo[3.3.0]octane



C11 H15 N3; Mol wt: 189.2605

ACTION – Nicotinic acetylcholine receptor modulator with potential utility in the treatment of CNS disorders including cognition disorders, anxiety, attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, depression and schizophrenia, as well as disorders related to smooth muscle contraction, neurodegeneration, inflammation, pain or withdrawal symptoms. Other specifically claimed heteroaryl diazabicycloalkanes include the following:



Compound	R1	R2	R3	Formula
307135	H	1-indolyl	perhydro-pyrrolo-[3,4- <i>c</i>]pyrrol-2-yl	C ₁₉ H ₂₀ N ₄
307136	OCH2CH2SH	H	perhydro-pyrrolo-[3,4- <i>c</i>]pyrrol-2-yl	C ₁₃ H ₁₉ N ₃ OS
307137	Br	H	perhydro-pyrrolo-[3,4- <i>c</i>]pyrrol-2-yl	C ₁₁ H ₁₄ BrN ₃
307138	H	OEt	3,7-diazabicyclo-[3.3.1]nonan-2-yl	C ₁₄ H ₂₁ N ₃ O
307139	H	CF3	3,7-diazabicyclo-[3.3.1]nonan-2-yl	C ₁₃ H ₁₆ F ₃ N ₃
307140	H	Et	3,7-diazabicyclo-[3.3.1]nonan-2-yl	C ₁₄ H ₂₁ N ₃
307141	H	OEt	3,7-diazabicyclo-[3.3.2]decan-3-yl	C ₁₅ H ₂₃ N ₃ O
307142	H	CF3	3,7-diazabicyclo-[3.3.2]decan-3-yl	C ₁₄ H ₁₈ F ₃ N ₃

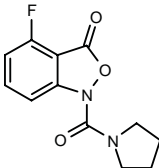
SOURCE – NeuroSearch.

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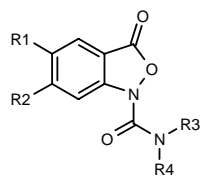
307310

4-Fluoro-1-(pyrrolidin-1-ylcarbonyl)-2,1-benzisoxazol-3(1*H*)-one



C12 H11 F N2 O3; Mol wt: 250.2279

ACTION – Inhibitor of *N*-acylpeptide hydrolase (ACPH, also known as acylaminoacyl-peptidase; IC₅₀ = 6 nM in rat brain homogenates), potentially useful in the treatment or prevention of CNS diseases, particularly cognitive disorders such as Alzheimer’s disease and other forms of dementia, cerebral infarct, brain trauma and pain. Other compounds from this series of 3-oxo-2,1-benzisoxazol-1(3*H*)-carboxamides include the following:



Compound	R1	R2	R3	R4	Formula
307311	H	H	Me	Me	C ₁₀ H ₁₀ N ₂ O ₃
307312	Me	H	-(CH2)4-		C ₁₃ H ₁₄ N ₂ O ₃
307313	F	F	-(CH2)4-		C ₁₂ H ₁₀ F ₂ N ₂ O ₃

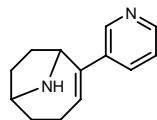
SOURCE – Bayer.

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307908

2-(3-Pyridyl)-9-azabicyclo[4.2.1]non-2-ene



C13 H16 N2; Mol wt: 200.2834

ACTION – A representative compound from a series of 9-azabicyclo[4.2.1]non-2-ene derivatives with affinity for nicotinic acetylcholine receptors (nAChR). It displayed K_i values of 0.43, 22.5, 89 and 3400 nM against α4β2, α3β4, α7 and α1β1δγ nAChR subtypes, respectively. Potentially useful for the treatment of cholinergic system-related conditions including Alzheimer’s disease, Tourette’s syndrome, cognitive disorders, drug dependencies and pain.

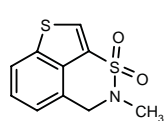
SOURCE – University of Bristol, Bristol (GB).

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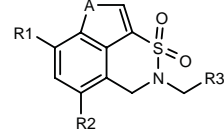
308098

2-Methyl-2,3-dihydrothieno[2,3,4-*ij*][2,3]benzothiazine 1,1-dioxide



C10 H9 N O2 S2; Mol wt: 239.3181

ACTION – Neuroprotective agent for the treatment and prevention of neurodegenerative disorders, particularly memory impairment and dementia, as well as cerebral ischemia and schizophrenia, a positive allosteric AMPA receptor modulator, as demonstrated in electrophysiological assays using AMPA receptor-expressing cells. Other exemplified tricyclic compounds include the following:



Compound	R1	R2	R3	A	Formula
308099	H	H	Me	-S-	C ₁₁ H ₁₁ NO ₂ S ₂
308100	Cl	H	H	-S-	C ₁₀ H ₈ ClNO ₂ S ₂
308102	H	F	H	-S-	C ₁₀ H ₈ FNO ₂ S ₂
308104	H	Cl	H	-S-	C ₁₀ H ₈ ClNO ₂ S ₂
308106	H	H	H	-N(Me)-	C ₁₁ H ₁₂ N ₂ O ₂ S

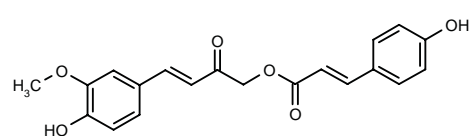
SOURCE – Boehringer Ingelheim.

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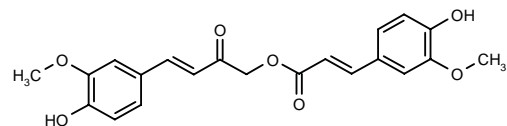
308585

3-(4-Hydroxyphenyl)-2-propenoic acid 4-(4-hydroxy-3-methoxyphenyl)-2-oxo-3-butenyl ester



C20 H18 O6; Mol wt: 354.3562

ACTION – Synthetic analogue of **calebin A**, a curcuminoid extracted from turmeric (*Curcuma longa*), with neuroprotective activity against β-amyloid-induced neurotoxicity in rat pheochromocytoma PC-12 and human neuroblastoma IMR-32 cells (EC₅₀ = 0.7 and 1.2 μg/ml, respectively); no cytotoxicity was seen at concentrations > 25 μg/ml. Potentially useful for the treat-ment of Alzheimer’s disease.



Calebin A [308583]: C21 H20 O7

SOURCE – University of Illinois, Chicago, IL (US).

REFERENCES

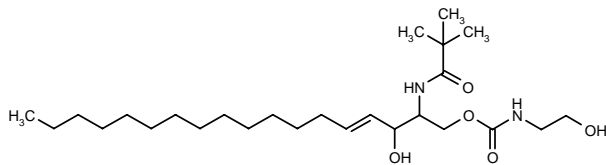
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2. Kim, D.S.H.L. and Kim, J.Y. *Total synthesis of calebin-A, preparation of its analogues, and their neuronal cell protectivity against β-amyloid insult*. Bioorg Med Chem Lett 2001, 11(18): 2541.

TREATMENT OF
CEREBROVASCULAR DISEASES

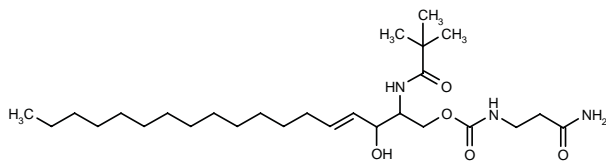
305566

N-(2-Hydroxyethyl)carbamic acid 2-(2,2-dimethylpropion-amido)-3-hydroxy-4-octadecenyl ester



C26 H50 N2 O5; Mol wt: 470.6900

ACTION – An inhibitor of neutral sphingomyelinase (IC₅₀ = 0.6 μM against enzyme from rat brain), potentially useful for the treatment or prevention of cerebrovascular disorders such as cerebral hemorrhage and cerebral infarction, head injuries, senile dementia, neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease, diabetes, obesity, arteriosclerosis, inflammatory and immunological diseases, cancer, renal diseases and heart diseases. Another exemplified compound from this series of sphingosine derivatives is:



305567: C27 H51 N3 O5

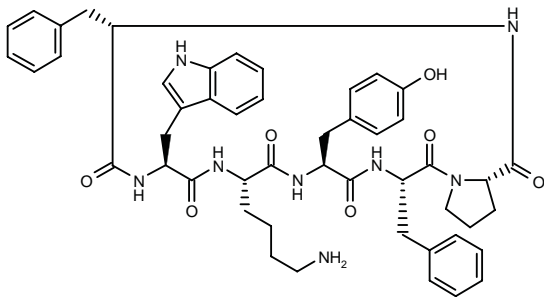
SOURCES – Sagami; Taisho.

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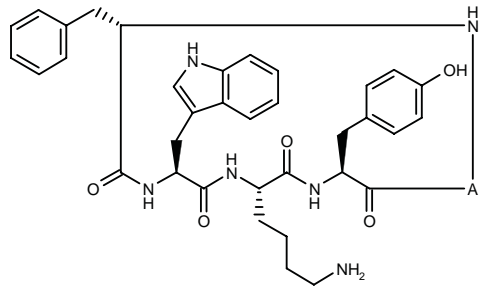
305608

Cyclo(L-phenylalanyl-L-tryptophyl-L-lysyl-L-tyrosyl-L-phenylalanyl-L-prolyl)



C49 H56 N8 O7; Mol wt: 869.0304

ACTION – Cyclic analogue of urotensin-II with potential for the treatment of conditions associated with urotensin-II imbalance, particularly stroke, as well as congestive heart failure, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, essential and pulmonary hypertension, chronic obstructive pulmonary disease (COPD), restenosis, asthma, neurogenic inflammation, metabolic vasculopathies, addiction, schizophrenia, anxiety, stress, depression, neuromuscular function disorders and diabetes. Other specifically claimed analogues are:



Compound	A	Formula
305610	-D-Pro-L-Pro-	C ₄₅ H ₅₄ N ₈ O ₇
305613	-NHCH ₂ CH ₂ CO-	C ₃₈ H ₄₅ N ₇ O ₆
305615	-NH(CH ₂) ₃ CO-	C ₃₉ H ₄₇ N ₇ O ₆
305616	-NH(CH ₂) ₄ CO-	C ₄₀ H ₄₉ N ₇ O ₆

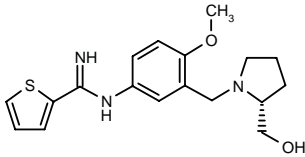
SOURCE – GlaxoSmithKline.

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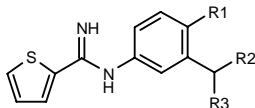
307499

N-[3-[2(*R*)-(Hydroxymethyl)pyrrolidin-1-ylmethyl]-4-methoxyphenyl]thiophene-2-carboxamide



C18 H23 N3 O2 S; Mol wt: 345.4647

ACTION – Inhibitor of nitric oxide synthase (NOS) with selectivity for the neuronal isoform, potentially useful in the treatment or prevention of hypoxia, ischemia, stroke, pain, anxiety, schizophrenia, Parkinson’s disease, Huntington’s disease, and migraine and other vascular headaches. Other specifically claimed compounds from this series of amidine derivatives include the following:



Compound	R1	R2	R3	Formula
307500	OMe	H	N(Me)CH2CH2OH	C ₁₆ H ₂₁ N ₃ O ₂ S
307501	OCH(Et)2	H	N(Me)CH2CH2OH	C ₂₀ H ₂₉ N ₃ O ₂ S
307502	i-PrO	H	NH(CH2)4OH	C ₁₉ H ₂₇ N ₃ O ₂ S
307503	cyclopentyl-O	H	N(Me)CH2CH2OH	C ₂₀ H ₂₇ N ₃ O ₂ S
307504	cyclopentyl	H	2(S)-(HOCH2)- -1-pyrrolidinyl	C ₂₂ H ₂₉ N ₃ OS
307506	OMe	Me	NHCH2CH2OH	C ₁₆ H ₂₁ N ₃ O ₂ S
307507	H	H	CH2NH- CH(Pr)CH2OH	C ₁₈ H ₂₅ N ₃ OS

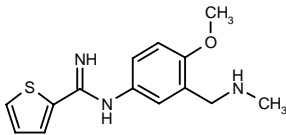
SOURCE – AstraZeneca.

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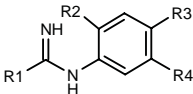
307508

N-[4-Methoxy-3-(methylaminomethyl)phenyl]thiophene-2-carboxamidine



C14 H17 N3 O S; Mol wt: 275.3743

ACTION – Inhibitor of nitric oxide synthase (NOS) with selectivity for the neuronal isoform, potentially useful in the treatment or prevention of hypoxia, ischemia, stroke, pain, anxiety, schizophrenia, Parkinson’s disease, Huntington’s disease, and migraine and other vascular headaches. Other specifically claimed compounds from this series of amidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
307509	3-thienyl	H	OMe	4-morpholinyl-CH2	C ₁₇ H ₂₁ N ₃ O ₂ S
307511	2-thienyl	OMe	H	CH2NHMe	C ₁₄ H ₁₇ N ₃ OS
307512	2-thienyl	H	OMe	CH2NH2	C ₁₃ H ₁₅ N ₃ OS
307513	2-thienyl	H	OMe	cyclopropyl-NHCH2	C ₁₆ H ₁₉ N ₃ OS
307514	2-thienyl	H	i-PrO	1-pyrrolidinyl-CH2	C ₁₉ H ₂₅ N ₃ OS
307515	2-thienyl	H	OPh	i-PrNHCH2	C ₂₁ H ₂₃ N ₃ OS
307516	2-thienyl	H	OMe	2-pyrrolidinyl	C ₁₆ H ₁₉ N ₃ OS

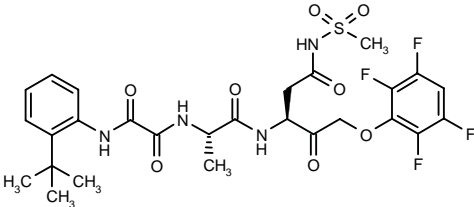
SOURCE – AstraZeneca.

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308044

N²-(2-*tert*-Butylphenylaminooxalyl)-N¹-[1 (S)-[N-(methylsulfonyl)carbamoylmethyl]-2-oxo-3-(2,3,5,6-tetrafluorophenoxy)propyl]-L-alaninamide



C27 H30 F4 N4 O8 S; Mol wt: 646.6120

ACTION – IL-1β-converting enzyme (ICE/ced-3) inhibitor (K_i = 0.004 μM) that also inhibits other cysteine proteases such as CPP32 (K_i = 0.856 μM), MCH-2 (K_i = 0.681 μM) and MCH-5 (K_i = 0.011 μM). Claimed to be useful for the treatment of inflammatory, immune and neurodegenerative diseases, the prevention of ischemic injury and unwanted apoptosis related to cells for use in transfusions, and the preservation of organs for transplantation.

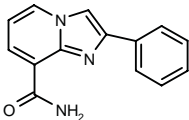
SOURCE – Idun Pharmaceuticals.

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1. Ternansky, R.J. et al. (Idun Pharmaceuticals, Inc.) *Inhibitors of the ICE/ced-3 family of cysteine proteases*. WO 0151462.

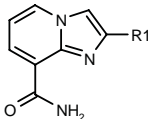
308275

2-Phenylimidazo[1,2-*a*]pyridine-8-carboxamide



C14 H11 N3 O; Mol wt: 237.2609

ACTION – Poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor, potentially useful for the treatment of neurological and neurodegenerative disorders including cerebral ischemia, traumatic brain injury, stroke, Huntington’s disease, Parkinson’s disease, Alzheimer’s disease and epilepsy, as well as renal ischemia, cardiac ischemia, myocardial infarction, cancer, sepsis, immunological disorders and diabetes mellitus. Other exemplified heterocyclic compounds include the following:



Compound	R1	Formula
308276	4-NO2-Ph	C ₁₄ H ₁₀ N ₄ O ₃
308278	4-NH2-Ph	C ₁₄ H ₁₂ N ₄ O
308279	2-benzothieryl	C ₁₆ H ₁₁ N ₃ OS
308280	4-Br-Ph	C ₁₄ H ₁₀ BrN ₃ O
308281	4-(1-imidazoly)-Ph	C ₁₇ H ₁₃ N ₅ O

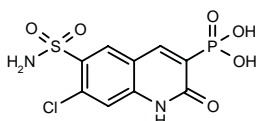
SOURCE – BASF.

REFERENCES

1. Lubisch, W. et al. (BASF AG) *Heterocyclic cpds. and their use as PARP inhibitors*. WO 0157038.

308513

(7-Chloro-2-oxo-6-sulfamoyl-1,2-dihydroquinolin-3-yl)-phosphonic acid



C9 H8 Cl N2 O6 P S; Mol wt: 338.6632

ACTION – AMPA/kainate receptor antagonist reported to be devoid of the nephrotoxicity associated with prior closely related AMPA antagonists. Potentially useful for the treatment of acute and chronic neurological disorders such as stroke, brain or spinal cord trauma, epilepsy and neurodegenerative disorders such as Alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis and Huntington's chorea.

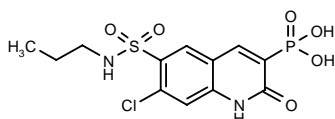
SOURCE – ADIR.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Derivs. of 6-sulfamoyl-3-quinolyl phosphonic acids, process for their preparation and pharmaceutical compsns. containing them*. EP 1125941, FR 2805260, JP 2001253892.

308515

[7-Chloro-2-oxo-6-(N-propylsulfamoyl)-1,2-dihydroquinolin-3-yl]phosphonic acid



C12 H14 Cl N2 O6 P S; Mol wt: 380.7436

ACTION – AMPA/kainate receptor antagonist reported to be devoid of the nephrotoxicity associated with prior closely related AMPA antagonists. Potentially useful for the treatment of acute and chronic neurological disorders such as stroke, brain or spinal cord trauma, epilepsy and neurodegenerative disorders such as Alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis and Huntington's chorea.

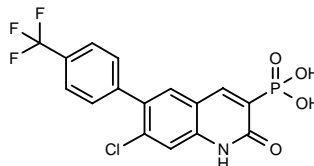
SOURCE – ADIR.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Derivs. of 6-amino or 6-hydrazinosulfonyl-3-quinolyl phosphonic acids, process for their preparation and pharmaceutical compsns. containing them*. EP 1125942, FR 2805261.

308517

[7-Chloro-2-oxo-6-[4-(trifluoromethyl)phenyl]-1,2-dihydroquinolin-3-yl]phosphonic acid



C16 H10 Cl F3 N O4 P; Mol wt: 403.6790

ACTION – AMPA/kainate receptor antagonist, potentially useful for the treatment of acute and chronic neurological disorders such as stroke, brain or spinal cord trauma, epilepsy and neurodegenerative disorders such as Alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis and Huntington's chorea.

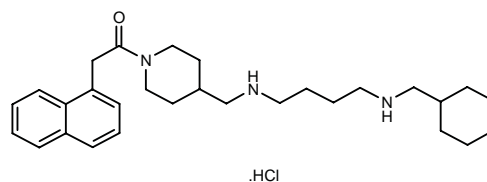
SOURCE – ADIR.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Derivs. of aryl or heteroaryl quinolinyphosphonic acids, process for their preparation and pharmaceutical compsns. containing them*. EP 1125940, FR 2805262, JP 2001278890.

308912

N¹-(Cyclohexylmethyl)-N⁴-[1-[2-(1-naphthyl)acetyl]-piperidin-4-ylmethyl]butane-1,4-diamine hydrochloride



.HCl

C29 H43 N3 O . HCl; Mol wt: 486.1396

ACTION – Diaminebutane derivative, a potent and selective Ca²⁺-permeable AMPA receptor antagonist (IC₅₀ = 0.25 μM for reducing kainate-induced inward current in *Xenopus* oocytes). Using recombinant receptors, it blocked the inward current via the Ca²⁺-permeable AMPA (GluR3) receptor by 65.8% at 3 μM, versus only 4.4% inhibition via Ca²⁺-impermeable AMPA receptors (GluR3+GluR2). In a model of transient global cerebral ischemia in gerbils, compound at a dose of 10 mg/kg i.p. produced significant protection against neuronal cell death; no hypotensive effect was seen in rats at a dose of 10 mg/kg i.v. Potentially useful for the treatment of cerebral ischemia.

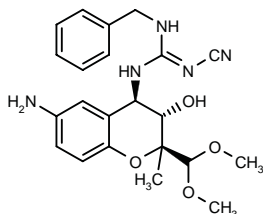
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Yoneda, Y. et al. *Synthesis of diaminobutane derivatives as potent CA²⁺-permeable AMPA receptor antagonists*. Bioorg Med Chem Lett 2001, 11(19): 2663.

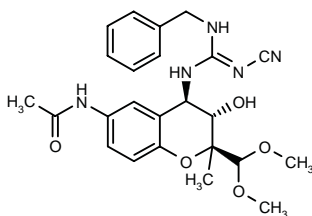
KR-31378^{1,2}**308659**

N-[6-Amino-2-(dimethoxymethyl)-3(*S*)-hydroxy-2(*S*)-methyl-3,4-dihydro-2*H*-1-benzopyran-4(*R*)-yl]-*N'*-benzyl-*N''*-cyanoguanidine



C22 H27 N5 O4; Mol wt: 425.4863

ACTION – Neuroprotective agent with antioxidant and potassium channel-modulating activities. *In vitro*, it protected cultured rat neurons against iron-induced oxidative injury, and *in vivo* in a model of transient cerebral ischemia in rats, it significantly reduced infarct volume at 24 h after occlusion. Cardioprotective effects have also been seen in rat and dog models of coronary artery occlusion and reperfusion, associated with minimal hypotensive effects. Compound showed dose-dependent pharmacokinetics in rats after both i.v. and p.o. administration; the AUC after i.p. and p.o. administration was comparable, indicating almost complete absorption from the gastrointestinal tract. **KR-31612** has been identified as a metabolite of KR-31378.

**KR-31612¹ [308691]:** C24 H29 N5 O5

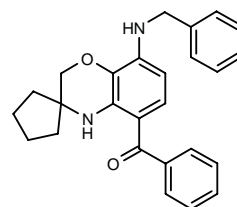
SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

- Kim, H.J. et al. Dose-dependent pharmacokinetics of a new neuroprotective agent for ischemia-reperfusion damage, KR-31378, in rats. *Biopharm Drug Dispos* 2000, 21(7): 279.
- Lee, B.H. et al. Cardioprotective effects of KR-31378, a cardioselective ATP-sensitive potassium channel activator, in rats and dogs. *FASEB J* 2001, 15(4, Part 1): Abst 462.1.

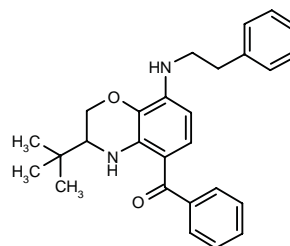
MISCELLANEOUS NEUROLOGIC DRUGS**S-24718^{*,1,3,4}****284013**

1-[8-(Benzylamino)-3,4-dihydrospiro[2*H*-1,4-benzoxazine-3,1'-cyclopentan]-5-yl]-1-phenylmethanone



C26 H26 N2 O2; Mol wt: 398.5034

ACTION – Neuroprotective antioxidant shown to prevent hypoxia-induced ATP depletion in neonatal rat astrocyte cultures at 1-100 μ M. In a model of cerebral palsy in newborn mice inoculated with *S*-bromowillardiine to induce excitotoxic lesions in the cortex and white matter, compound produced significant neuroprotection at doses of 1 and 10 mg/kg i.p. Potentially useful for the treatment of cerebral palsy and other neurodegenerative diseases. Another 8-alkylamino-1,4-benzoxazine is:

**S-24429¹⁻⁴ [309022]:** C27 H30 N2 O2**SOURCE** – Servier.**REFERENCES**

- Fleury, M.B. et al. (ADIR et Cie.) Novel 8-amino-1,4-benzoxazine cpds., preparation method and pharmaceutical compns. containing them. FR 2779144, WO 9962889.
- Largerion, M. and Fleury, M.-B. A convenient two-step one-pot electrochemical synthesis of novel 8-amino-1,4-benzoxazine derivatives possessing anti-stress oxidative properties. *Tetrahedron Lett* 1998, 39(49): 8999.
- Largerion, M. et al. Synthesis and *in vitro* evaluation of new 8-amino-1,4-benzoxazine derivatives as neuroprotective antioxidants. *J Med Chem* 1999, 42(24): 5043.
- Largerion, M. et al. The neuroprotective activity of 8-alkylamino-1,4-benzoxazine antioxidants. *Eur J Pharmacol* 2001, 424(3): 189.

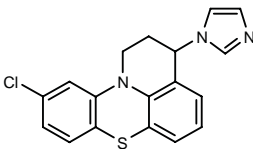
*Identified compound **284013** (see **284012**) *Drug Data Rep* 2000, 022(03): 0232.

RESPIRATORY DRUGS

ASTHMA THERAPY

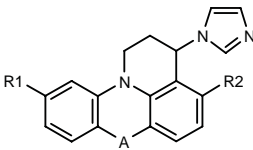
305505

10-Chloro-3-(1*H*-imidazol-1-yl)-2,3-dihydro-1*H*-pyrido-[3,2,1-*k*]phenothiazine



C18 H14 Cl N3 S; Mol wt: 339.8486

ACTION – An inhibitor of phosphodiesterase type 7 (PDE7) and TNF-α production, potentially useful for the treatment of asthma, allergic disorders, chronic bronchitis, atopic dermatitis, psoriasis and other skin disorders, inflammatory and autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, Crohn’s disease, ulcerative colitis and diabetes mellitus, osteoporosis, transplant rejection, cachexia, cancer, sepsis, memory impairment, atherosclerosis and AIDS. Other exemplified compounds from this series of substituted imidazole derivatives include the following:



Compound	R1	R2	A	Formula
305506	H	Cl	S	C ₁₈ H ₁₄ ClN ₃ S
305507	OMe	H	S	C ₁₉ H ₁₇ N ₃ OS
305508	OPr	H	S	C ₂₁ H ₂₁ N ₃ OS
305509	SMe	H	S	C ₁₉ H ₁₇ N ₃ S ₂
305510	F	H	S	C ₁₈ H ₁₄ FN ₃ S
305511	Cl	Cl	S	C ₁₈ H ₁₃ Cl ₂ N ₃ S
305512	CF ₃	H	S	C ₁₉ H ₁₄ F ₃ N ₃ S
305513	H	cyclopentyl-O	S	C ₂₃ H ₂₃ N ₃ OS
305514	Cl	H	O	C ₁₈ H ₁₄ ClN ₃ O
305515	Cl	H	SO ₂	C ₁₈ H ₁₄ ClN ₃ O ₂ S

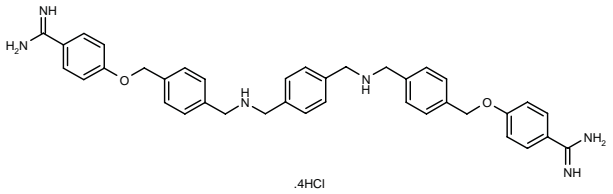
SOURCE – Merck KGaA.

REFERENCES

1. Eggenweiler, H.M. et al. (Merck Patent GmbH) *Imidazole cpds. used as phosphodiesterase VII inhibitors*. DE 19954707, WO 0136425.

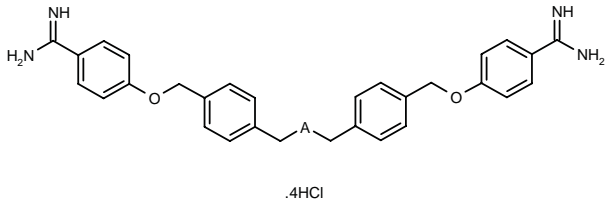
305527

4,4'-[(1,4-Phenylene)bis(methyleneiminomethylene)-bis(1,4-phenylene)bis(methyleneoxy)]bis(benzamidine) tetrahydrochloride

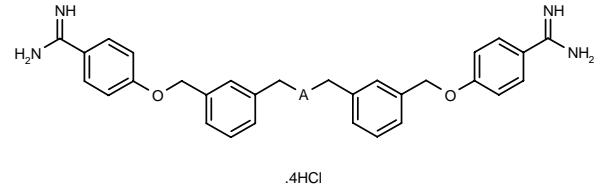


C38 H40 N6 O2 . 4HCl; Mol wt: 758.6176

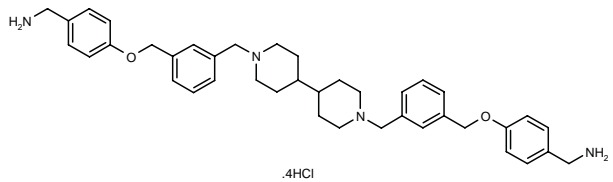
ACTION – Agent for the treatment or prevention of inflammatory and allergic disorders such as bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria, ulcerative colitis, Crohn’s disease, anaphylactic shock, septic shock, adult respiratory distress syndrome and arthritis, as well as fibrosis, lupus erythematosus, scleroderma, arteriosclerosis, psoriasis and cancer, an inhibitor of tryptase (IC₅₀ = 0.59 nM against recombinant human β-tryptase). Other specifically claimed compounds from this series of bis-basic derivatives are:



Compound	A	Formula
305528	-NH(CH ₂) ₆ NH-	C ₃₆ H ₄₄ N ₆ O ₂ ·4HCl
305533	-4,4'-bipiperidin-1,1'-yl-	C ₄₀ H ₄₈ N ₆ O ₂ ·4HCl



Compound	A	Formula
305530	-NHCH ₂ -1,4-cyclohexanediyl-CH ₂ NH-	C ₃₈ H ₄₆ N ₆ O ₂ ·4HCl
305531	-4,4'-bipiperidin-1,1'-yl-	C ₄₀ H ₄₈ N ₆ O ₂ ·4HCl
305532	-NH(CH ₂) ₇ NH-	C ₃₇ H ₄₆ N ₆ O ₂ ·4HCl
305534	-NH(CH ₂) ₆ NH-	C ₃₆ H ₄₄ N ₆ O ₂ ·4HCl
305535	-NH(CH ₂) ₅ NH-	C ₃₅ H ₄₂ N ₆ O ₂ ·4HCl
305536	-NHC(Me) ₂ CH ₂ CH ₂ C(Me) ₂ NH-	C ₃₈ H ₄₈ N ₆ O ₂ ·4HCl
305537	-NHCH ₂ -1,4-Ph-CH ₂ NH-	C ₃₈ H ₄₀ N ₆ O ₂ ·4HCl
305538	-NHC(Me) ₂ (CH ₂) ₄ C(Me) ₂ NH-	C ₄₀ H ₅₂ N ₆ O ₂ ·4HCl



305540: C40 H50 N4 O2 . 4HCl

SOURCE – Boehringer Ingelheim.

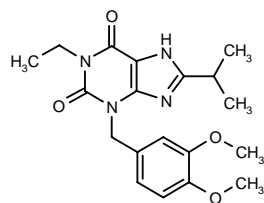
REFERENCES

1. Anderskewitz, R. et al. (Boehringer Ingelheim Pharma KG) *Bis-basic cpds. for use as tryptase inhibitors, method for producing the same and their use as medicaments.* DE 19955476, WO 0136374.

305570

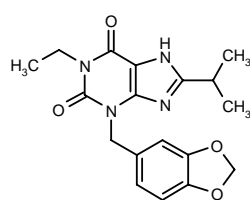
3-(3,4-Dimethoxybenzyl)-1-ethyl-8-isopropyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione

3-(3,4-Dimethoxybenzyl)-1-ethyl-8-isopropylxanthine



C19 H24 N4 O4; Mol wt: 372.4226

ACTION – Agent for the treatment of asthma, allergies, atopic diseases and rhinitis, a selective phosphodiesterase type 4 (PDE4) inhibitor. Another exemplified compound is:



305929: C18 H20 N4 O4

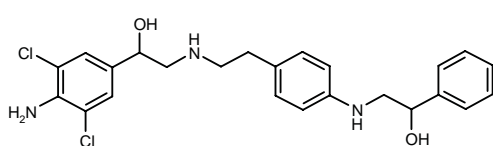
SOURCE – Eurocelltique.

REFERENCES

1. Chasin, M. et al. (Eurocelltique SA) *3-(Arylalkyl) xanthines.* US 6248746.

306350

1-(4-Amino-3,5-dichlorophenyl)-2-[2-[4-(2-hydroxy-2-phenylethylamino)phenyl]ethylamino]ethanol



C24 H27 Cl2 N3 O2; Mol wt: 460.4023

ACTION – A representative compound from a series of α -aminoalcohol derivatives that act as β_2 -adrenoceptor agonists or partial agonists. Potentially useful for the treatment and prevention of respiratory diseases, especially asthma and chronic obstructive pulmonary disease, as well as other conditions mediated by this receptor such as nervous system injury, premature labor, obesity and diabetes.

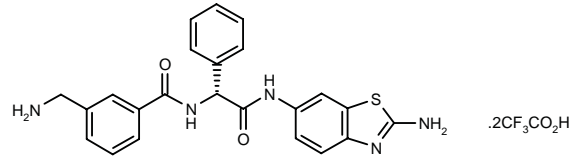
SOURCE – Advanced Medicine.

REFERENCES

1. Moran, E.J. et al. (Advanced Medicine, Inc.) *β_2 -Adrenergic receptor agonists.* WO 0142193.

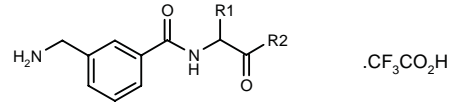
307151

*N*¹-(2-Aminobenzothiazol-6-yl)-*N*²-[*N*-[3-(aminomethyl)-benzoyl]-*D*-phenylglycynamide bis(trifluoroacetate)

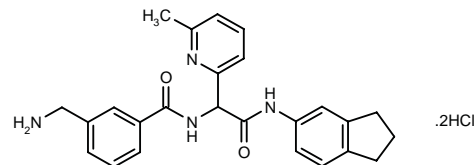


C23 H21 N5 O2 S . 2 C2 H F3 O2; Mol wt: 659.5617

ACTION – Tryptase inhibitor with potential in the treatment or prevention of asthma and other allergic and inflammatory conditions mediated by tryptase such as allergic rhinitis, skin conditions such as eczema, psoriasis, atopic dermatitis and urticaria, rheumatoid arthritis, conjunctivitis, inflammatory bowel disease, neurogenic inflammation, atherosclerosis and cancer. Other exemplified compounds from this series of 3-(aminomethyl)benzene derivatives include the following:



Compound	R1	R2	Formula
307152	(R)-Ph	1-Pip	C ₂₁ H ₂₅ N ₃ O ₂ .C ₂ HF ₃ O ₂
307153	(R)-Ph	2-[N-Ac-D-Ala-]- -2,3-dihydro-6-indolyl-NH	C ₂₉ H ₃₁ N ₅ O ₄ .C ₂ HF ₃ O ₂
307154	(R)-Ph	1-[2-(CHONH)-4-thiazolyl-CH2CO]- -2,3-dihydro-6-indolyl-NH	C ₃₀ H ₂₈ N ₆ O ₄ S .C ₂ HF ₃ O ₂
307155	(R)-Ph	8-AcO-2-quinolyl-NH	C ₂₇ H ₂₄ N ₄ O ₄ .C ₂ HF ₃ O ₂
307156	(R)-Ph	3-(cyclopropyl-CH2NHCO)- -4,5,6,7-tetrahydro-2-benzothienyl-NH	C ₂₉ H ₃₂ N ₄ O ₃ S .C ₂ HF ₃ O ₂
307157	(R,S)-Ph	1-(EtSO2)-2,3-dihydro-6-indolyl-NH	C ₂₆ H ₂₈ N ₄ O ₄ S .C ₂ HF ₃ O ₂
307159	(R,S)-Ph	2-benzothiazolyl-NH	C ₂₃ H ₂₀ N ₄ O ₂ S .C ₂ HF ₃ O ₂



307158: C25 H26 N4 O2 . 2HCl

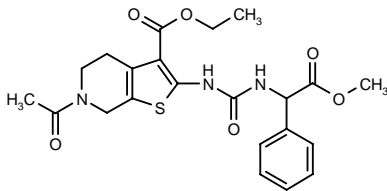
SOURCE – Protherics.

REFERENCES

1. Lively, S.E. et al. (Protherics plc) *Serine protease inhibitors.* WO 0144226.

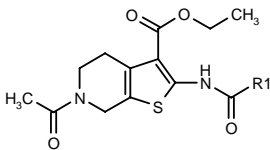
307288

6-Acetyl-2-[3-(2-methoxy-2-oxo-1-phenylethyl)ureido]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid ethyl ester



C22 H25 N3 O6 S; Mol wt: 459.5205

ACTION – Inhibitor of TNF- α production (IC_{50} = 0.90 μ M in lipopolysaccharide-stimulated rat blood) with potential for the treatment of inflammatory, autoimmune and allergic diseases. Other exemplified compounds from this series of 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines include the following:



Compound	R1	Formula
307289	4-morpholinyl	C ₁₇ H ₂₃ N ₃ O ₅ S
307956	N(Et)2	C ₁₇ H ₂₆ N ₃ O ₄ S

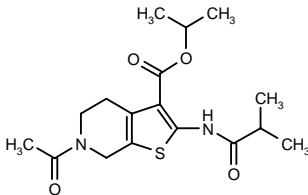
SOURCE – Nikken Chemicals.

REFERENCES

1. Fujita, S. et al. (Nikken Chemicals Co., Ltd.) 4,5,6,7-Tetrahydrothieno[2,3-*c*]pyridine derivs. JP 2001158789.

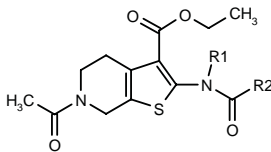
307290

6-Acetyl-2-(isobutyramido)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid isopropyl ester



C17 H24 N2 O4 S; Mol wt: 352.4526

ACTION – Inhibitor of TNF- α production (IC_{50} = 7.10 μ M in lipopolysaccharide-stimulated rat blood) with potential for the treatment of inflammatory, autoimmune and allergic diseases. Other exemplified compounds from this series of 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines include the following:



Compound	R1	R2	Formula
307291	H	Me	C ₁₄ H ₁₈ N ₂ O ₄ S
307292	H	Et	C ₁₅ H ₂₀ N ₂ O ₄ S
307293	H	t-Bu	C ₁₇ H ₂₄ N ₂ O ₄ S
307294	H	cyclopropyl	C ₁₆ H ₂₀ N ₂ O ₄ S
307295	Me	Et	C ₁₆ H ₂₂ N ₂ O ₄ S

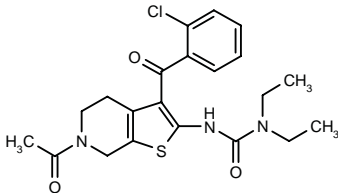
SOURCE – Nikken Chemicals.

REFERENCES

1. Inada, H. et al. (Nikken Chemicals Co., Ltd.) 4,5,6,7-Tetrahydrothieno[2,3-*c*]pyridine cpds. JP 2001151780.

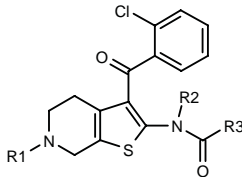
307296

N-[6-Acetyl-3-(2-chlorobenzoyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]-*N*',*N*'-diethylurea



C21 H24 Cl N3 O3 S; Mol wt: 433.9576

ACTION – Inhibitor of TNF- α production (IC_{50} = 0.54 μ M in lipopolysaccharide-stimulated rat blood) with potential for the treatment of inflammatory, autoimmune and allergic diseases. Other exemplified compounds from this series of 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines include the following:



Compound	R1	R2	R3	Formula
307297	Et	H	i-Pr	C ₂₀ H ₂₃ ClN ₂ O ₂ S
307298	Et	Et	i-Pr	C ₂₂ H ₂₇ ClN ₂ O ₂ S
307299	cyclopropyl-CO	H	cyclopropyl	C ₂₂ H ₂₁ ClN ₂ O ₃ S

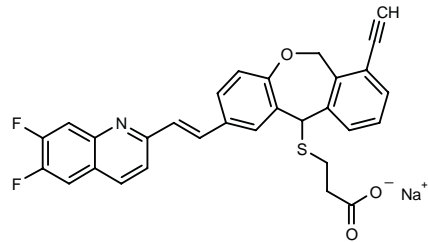
SOURCE – Nikken Chemicals.

REFERENCES

1. Inada, H. et al. (Nikken Chemicals Co., Ltd.) 4,5,6,7-Tetrahydrothieno[2,3-*c*]pyridine cpds. JP 2001151779.

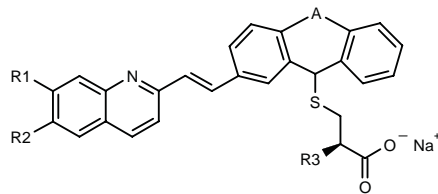
307455

3-[2-(*E*)-(6,7-Difluoroquinolin-2-yl)vinyl]-7-ethynyl-6,11-dihydrodibenzo[*b,e*]oxepin-11-ylsulfany]propionic acid sodium salt



C30 H20 F2 N Na O3 S; Mol wt: 535.5440

ACTION – Leukotriene antagonist with a p*K*_i of 9.8 against the leukotriene D₄ (LTD₄ or CysLT₁) receptor and an ED₅₀ of 0.0008 mg/kg p.o. in the LTD₄-induced airways constriction test in guinea pigs. Potentially useful as an antiallergic or antiinflammatory agent. Other exemplified tricyclic compounds are:



Compound	R1	R2	R3	A	Formula
307456	Cl	F	H	-OCH2-	C ₂₈ H ₂₀ ClFNNaO ₃ S
307458	F	F	H	-OCH2-	C ₂₈ H ₂₀ F ₂ NNaO ₃ S
307459	F	H	Me	-OCH2-	C ₂₉ H ₂₃ FNNaO ₃ S
307460	F	F	H	-CH2O-	C ₂₈ H ₂₀ F ₂ NNaO ₃ S

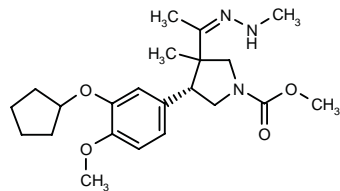
SOURCE – Ube.

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1. Kuroki, Y. et al. (Ube Industries, Ltd.) *Tricyclic cpds.* WO 0147889.

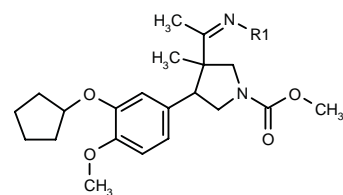
307490

4(*R*)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[1-(*N*-methylhydrazono)ethyl]pyrrolidine-1-carboxylic acid methyl ester



C22 H33 N3 O4; Mol wt: 403.5197

ACTION – Agent for the treatment and prevention of allergic, autoimmune and inflammatory diseases, a potent and selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 2.2 nM against human recombinant enzyme), also proven to inhibit TNF-α production (EC₅₀ = 2.2 nM in lipopolysaccharide-stimulated human peripheral blood lymphocytes). It is reported to be devoid of the adverse CNS side effects associated with prior PDE4 inhibitors. Other exemplified compounds from this series of hydrazone and oxime derivatives of pyrrolidine include the following:



Compound	R1	Isomer	Formula
307491	NHMe	4S	C ₂₂ H ₃₃ N ₃ O ₄
307493	OH	3S,4S	C ₂₁ H ₃₀ N ₂ O ₅
307494	OH	3R,4R	C ₂₁ H ₃₀ N ₂ O ₅

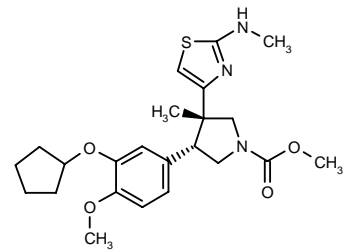
SOURCE – Icos.

REFERENCES

1. Fowler, K.W. et al. (Icos Corp.) *Hydrazone and oxime derivs. of pyrrolidine as AMP-specific phosphodiesterase inhibitors.* WO 0146136.

307495

4(*R*)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(*S*)-methyl-3-[2-(methylamino)thiazol-4-yl]pyrrolidine-1-carboxylic acid methyl ester



C23 H31 N3 O4 S; Mol wt: 445.5809

ACTION – Agent for the treatment and prevention of allergic, autoimmune and inflammatory diseases, a selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 4.731 μM against human recombinant enzyme). A representative compound from a series of 3-thiazol-4-yl-pyrrolidine derivatives.

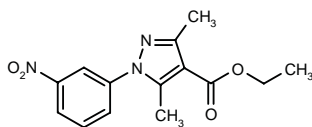
SOURCE – Icos.

REFERENCES

1. Fowler, K.W. and Odingo, J. (Icos Corp.) *3-Thiazol-4-yl-pyrrolidine derivs. as AMP-specific phosphodiesterase inhibitors.* US 6313156, WO 0146184.

307498

3,5-Dimethyl-1-(3-nitrophenyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester



C14 H15 N3 O4; Mol wt: 289.2895

ACTION – Agent for the treatment and prevention of allergic, autoimmune and inflammatory diseases, a potent and selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.10 µM against human recombinant enzyme), also proven to inhibit lipopolysaccharide-stimulated TNF-α production in mice (70 and 100% inhibition at 10 and 100 mg/kg i.p., respectively) while being devoid of the sedative side effects typically associated with prior PDE4 inhibitors. A representative compound from a series of pyrazole derivatives.

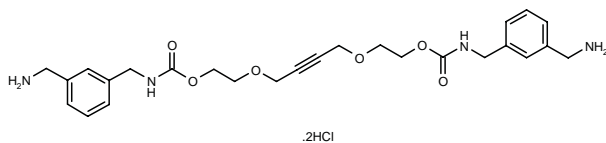
SOURCE – Icos.

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1. Martins, T.J. et al. (Icos Corp.) *Pyrazole cyclic AMP-specific PDE inhibitors*. WO 0146172.

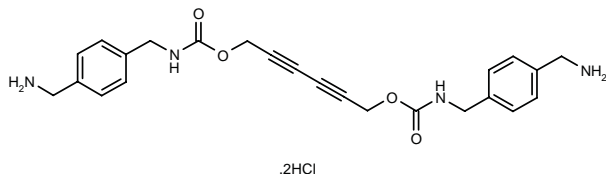
307517

Bis[*N*-[3-(aminomethyl)benzyl]carbamic acid] (2-butyne-1,4-diyl)bis(oxy)bis(ethylene) diester dihydrochloride

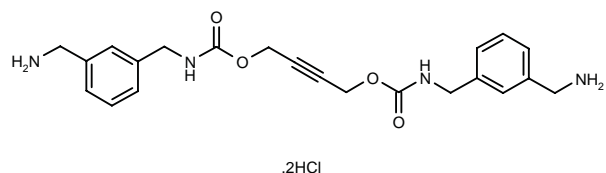


C26 H34 N4 O6 . 2HCl; Mol wt: 571.4984

ACTION – Human mast cell tryptase inhibitor (K_{iapp} = 0.006 µM), with potential for the treatment of airways disorders such as asthma, chronic obstructive pulmonary disease and bronchitis, as well as interstitial lung disorders, allergic rhinitis, allergic conjunctivitis, arthritis, multiple sclerosis, psoriasis and inflammatory bowel disease. Other exemplified compounds from this series of alkynyl derivatives are:



307519: C24 H26 N4 O4 . 2HCl



307520: C22 H26 N4 O4 . 2HCl

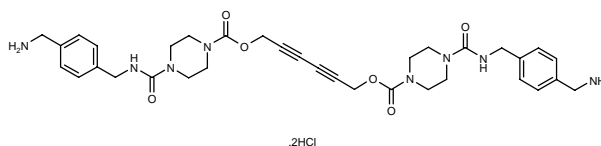
SOURCE – Byk Gulden.

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1. Bär, T. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Tryptase inhibitors*. WO 0146128.

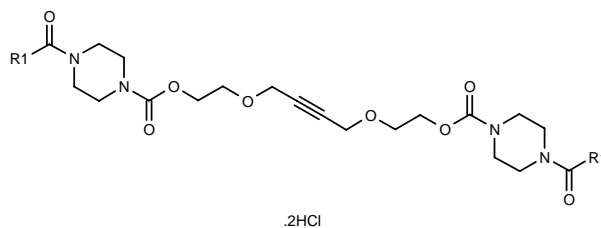
307521

Bis[4-[*N*-[4-(aminomethyl)benzyl]carbamoyl]piperazine-1-carboxylic acid] (2,4-hexadiyne-1,6-diyl) diester dihydrochloride

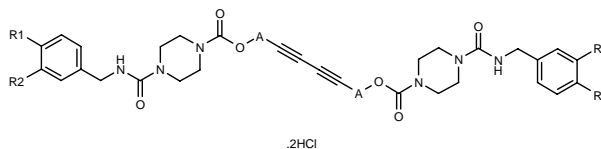


C34 H42 N8 O6 . 2HCl; Mol wt: 731.6776

ACTION – Human mast cell tryptase inhibitor (K_{iapp} = 0.00025 µM), with potential for the treatment of airways disorders such as asthma, chronic obstructive pulmonary disease and bronchitis, as well as interstitial lung disorders, allergic rhinitis, allergic conjunctivitis, arthritis, multiple sclerosis, psoriasis and inflammatory bowel disease. Other exemplified compounds from this series of alkynyl derivatives are:



Compound	R1	Formula
307522	trans-4-(NH ₂ CH ₂)-cyclohexyl	C ₃₄ H ₅₆ N ₆ O ₈ ·2HCl
307523	4-(NH ₂ CH ₂)-PhCH ₂ NH	C ₃₆ H ₅₀ N ₈ O ₈ ·2HCl
307524	3-(NH ₂ CH ₂)-PhCH ₂ NH	C ₃₆ H ₅₀ N ₈ O ₈ ·2HCl



Compound	R1	R2	A	Formula
307525	CH ₂ NH ₂	H	-(CH ₂) ₄ -	C ₄₀ H ₅₄ N ₈ O ₆ ·2HCl
307526	H	CH ₂ NH ₂	-(CH ₂) ₄ -	C ₄₀ H ₅₄ N ₈ O ₆ ·2HCl
307527	H	CH ₂ NH ₂	-CH ₂ -	C ₃₄ H ₄₂ N ₈ O ₆ ·2HCl

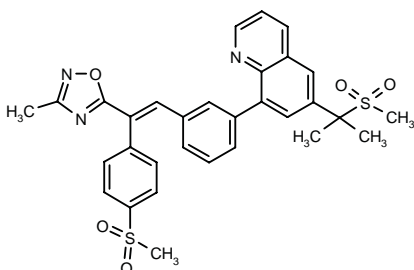
SOURCE – Byk Gulden.

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307617

6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]vinyl]-phenyl]quinoline



C31 H29 N3 O5 S2; Mol wt: 587.7181

ACTION – Potent phosphodiesterase type 4 (PDE4) inhibitor reported to inhibit human recombinant enzyme with an IC_{50} value in the range 0.14-10.24 nM. Potentially useful for the treatment of asthma, chronic bronchitis, chronic obstructive pulmonary disease, psoriasis and arthritis, among other inflammatory disorders. A representative compound from a series of substituted 8-arylquinoline derivatives.

SOURCE – Merck Frosst.

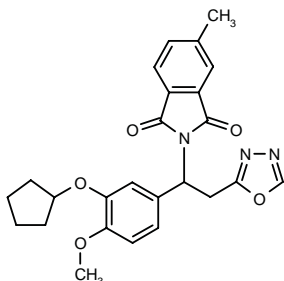
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1. Deschenes, D. et al. (Merck Frosst Canada Inc.) *Subst. 8-arylquinoline phosphodiesterase-4 inhibitors*. WO 0146151.

307627

2-[1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methyl-2,3-dihydro-1H-isindole-1,3-dione

N-[1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylphthalimide



C25 H25 N3 O5; Mol wt: 447.4885

ACTION – An inhibitor of TNF- α production, NF- κ B activation, phosphodiesterases (particularly PDE4) and/or angiogenesis, reported to be useful for the treatment of cancer and inflammatory and autoimmune diseases. A representative compound from a series of substituted 1,3,4-oxadiazoles.

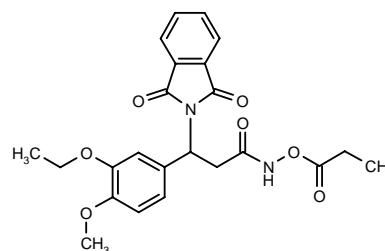
SOURCE – Celgene.

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1. Man, H.-W. and Muller, G. (Celgene Corp.) *Subst. 1,3,4-oxadiazoles and a method of reducing TNF α levels*. WO 0146183.

307629

3-(1,3-Dioxo-2,3-dihydro-1H-isindol-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propionohydroxamic acid propionyl mixed anhydride



C23 H24 N2 O7; Mol wt: 440.4496

ACTION – An inhibitor of TNF- α production, NF- κ B activation, phosphodiesterases (particularly PDE4) and/or angiogenesis, reported to be useful for the treatment of cancer and inflammatory and autoimmune diseases. A representative compound from a series of substituted acylhydroxamic acids.

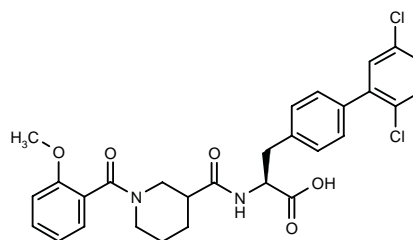
SOURCE – Celgene.

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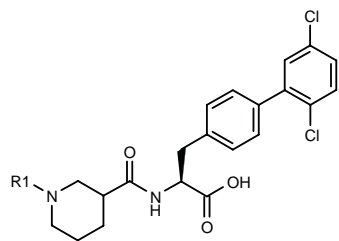
307841

4-(2,5-Dichlorophenyl)-N-[1-(2-methoxybenzoyl)piperidin-3-ylcarbonyl]-L-phenylalanine



C29 H28 Cl2 N2 O5; Mol wt: 555.4552

ACTION – Integrin antagonist particularly active against $\alpha_4\beta_1$, $\alpha_4\beta_7$ and/or $\alpha_9\beta_1$ integrins, proven to inhibit the adhesion of Jurkat cells to VCAM-1 with an $IC_{50} < 0.5 \mu$ M. Potentially useful for the treatment of inflammatory, autoimmune and immune diseases including arteriosclerosis, asthma, allergy, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, transplant rejection and arthritis. Other exemplified β -amino acid compounds are:



Compound	R1	Formula
307842	cyclopentyl-OCO	C ₂₇ H ₃₀ Cl ₂ N ₂ O ₅
307843	SO ₂ CH ₂ Ph	C ₂₈ H ₂₈ Cl ₂ N ₂ O ₅ S
307845	6-(2-Pyr-CH ₂ NH)-5-F-4-pyrimidinyl	C ₃₁ H ₂₈ Cl ₂ FN ₆ O ₃
307846	6-(1-Piz)-5-F-4-pyrimidinyl	C ₂₉ H ₃₁ Cl ₂ FN ₆ O ₃
307847	6-(4-morpholinyl)-5-F-4-pyrimidinyl	C ₂₉ H ₃₀ Cl ₂ FN ₅ O ₄

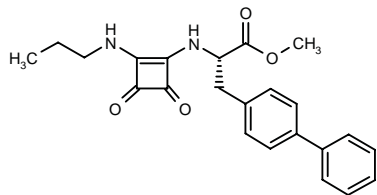
SOURCE – Bayer.

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1. Lehmann, T. et al. (Bayer AG) *β-Amino acid cpds. as integrin antagonists*. DE 19962936, WO 0147887.

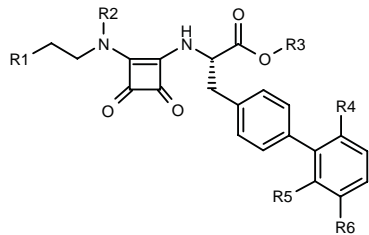
307866

N-[3,4-Dioxo-2-(propylamino)-1-cyclobuten-1-yl]-4-phenyl-L-phenylalanine methyl ester

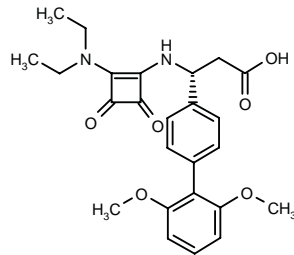


C₂₃ H₂₄ N₂ O₄; Mol wt: 392.4526

ACTION – Selective α_4 integrin inhibitor reported to be selective for $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ integrins, and thus potentially useful for the treatment of arthritis, multiple sclerosis, allograft rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other exemplified squaric acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
307867	H	Et	Me	OMe	OMe	H	C ₂₆ H ₃₀ N ₂ O ₆
307868	H	Et	H	H	OMe	H	C ₂₄ H ₂₆ N ₂ O ₅
307869	Me	H	H	H	OMe	H	C ₂₃ H ₂₄ N ₂ O ₅
307871	Me	H	H	H	CF ₃	H	C ₂₃ H ₂₁ F ₃ N ₂ O ₄
307872	Me	H	H	OMe	H	OMe	C ₂₄ H ₂₆ N ₂ O ₆
307873	Me	H	H	OMe	H	CHO	C ₂₄ H ₂₄ N ₂ O ₆



307870: C₂₅ H₂₈ N₂ O₆

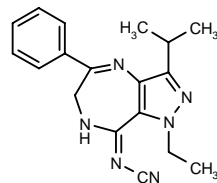
SOURCE – Celltech Group.

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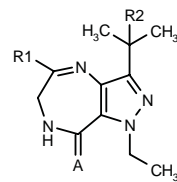
307964

N-(1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-ylidene)cyanamide



C₁₈ H₂₀ N₆; Mol wt: 320.3980

ACTION – A selective phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 0.12 nM) shown to inhibit lipopolysaccharide-induced TNF- α production in a rat model of inflammation. This compound is potentially useful for the treatment of inflammatory and allergic diseases, particularly chronic obstructive bronchopneumopathy and asthma. Other exemplified substituted pyrazolo[4,3-e]-diazepines include the following:



Compound	R1	R2	A	Formula
307965	4-Me-Ph	H	O	C ₁₈ H ₂₂ N ₄ O
307966	Ph	Me	N(CN)	C ₁₉ H ₂₂ N ₆
307967	t-Bu	H	N(CN)	C ₁₆ H ₂₄ N ₆
307968	4-Me-Ph	H	N(CN)	C ₁₉ H ₂₂ N ₆

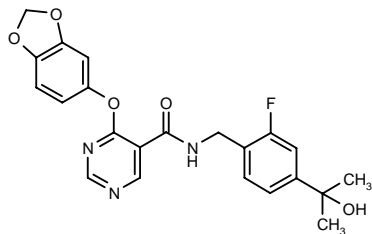
SOURCE – Pfizer.

REFERENCES

1. Burnouf, C. et al. (Pfizer Inc.) *Novel subst. pyrazolo[4,3-e]diazepines, pharmaceutical compsns. containing them, use as medicinal products and processes for preparing them*. FR 2803299, WO 0149689.

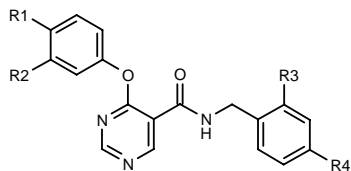
308145

4-(1,3-Benzodioxol-5-yloxy)-N-[2-fluoro-4-(1-hydroxy-1-methylethyl)benzyl]pyrimidine-5-carboxamide



C22 H20 F N3 O5; Mol wt: 425.4140

ACTION – Selective inhibitor of phosphodiesterase type 4 (PDE4), potentially useful for the treatment and prevention of a broad range of disorders mediated by PDE4 such as asthma, bronchitis, chronic obstructive airways disease, allergic rhinitis, dermatitis, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, transplant rejection and viral infections. Other exemplified compounds from this series of pyrimidine carboxamides are:



Compound	R1	R2	R3	R4	Formula
308147	-OCH2O-		H	CH(Me)2OH	C ₂₂ H ₂₁ N ₃ O ₅
308148	F	H	Cl	H	C ₁₈ H ₁₃ ClFN ₃ O ₂

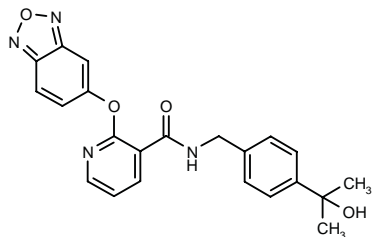
SOURCE – Pfizer.

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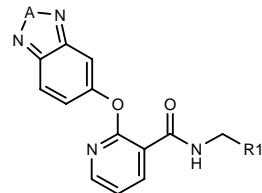
308151

2-(2,1,3-Benzoxadiazol-5-yloxy)-N-[4-(1-hydroxy-1-methylethyl)benzyl]pyridine-3-carboxamide



C22 H20 N4 O4; Mol wt: 404.4240

ACTION – Selective inhibitor of phosphodiesterase type 4 (PDE4), potentially useful for the treatment and prevention of a broad range of disorders mediated by PDE4 such as asthma, bronchitis, chronic obstructive airways disease, allergic rhinitis, dermatitis, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, transplant rejection and viral infections. Other exemplified nicotinamide benzofused-heterocyclic compounds include the following:



Compound	R1	A	Isomer	Formula
308152	4-[C(Me)2OH]-cyclohexyl	O	trans	C ₂₂ H ₂₆ N ₄ O ₄
308154	5-[MeCH(OH)]-2-thiazolyl	O	racemic	C ₁₉ H ₁₆ N ₄ O ₄ S
308159	4-[MeCH(OH)]-Ph	O	racemic	C ₂₁ H ₁₈ N ₄ O ₄
308160	4-[C(Me)2OH]-1-cyclohexen-1-yl	O	(+)-(R)	C ₂₂ H ₂₄ N ₄ O ₄
308162	2-F-4-[1-OH-cyclopropyl]-Ph	O		C ₂₂ H ₁₇ FN ₄ O ₄
308164	4-[i-PrC(OH)(Me)]-Ph	O	racemic	C ₂₄ H ₂₄ N ₄ O ₄
308165	2-F-4-[C(Me)2OH]-Ph	S		C ₂₂ H ₁₉ FN ₄ O ₃ S

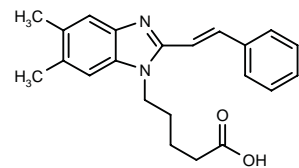
SOURCE – Pfizer.

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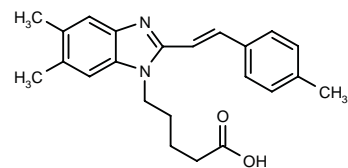
308638

5-[5,6-Dimethyl-2-(2-phenylvinyl)-1H-benzimidazol-1-yl]pentanoic acid



C22 H24 N2 O2; Mol wt: 348.4436

ACTION – A chymase inhibitor reported to be active against human recombinant mast cell chymase (IC₅₀ = 1-10 μM) and considered to have potential in the treatment of inflammation, allergy, respiratory and circulatory diseases, and bone and cartilage disorders. Another exemplified benzimidazole derivative is:



308639: C23 H26 N2 O2

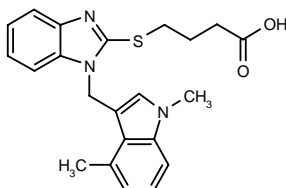
SOURCE – Teijin.

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1. Matsumoto, Y. and Saito, H. (Teijin Ltd.) *Benzimidazole derivs.* JP 2001192372.

308640

4-[1-(1,4-Dimethyl-1*H*-indol-3-ylmethyl)-1*H*-benzimidazol-2-ylsulfanyl]butyric acid



C22 H23 N3 O2 S: Mol wt: 393.5087

ACTION – Human mast cell chymase inhibitor (IC_{50} = 1-10 nM) with good metabolic stability, potentially useful for the treatment of inflammatory, allergic, respiratory, circulatory and bone diseases. A representative compound from a series of benzimidazole derivatives.

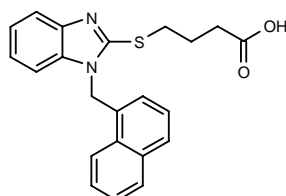
SOURCE – Teijin.

REFERENCES

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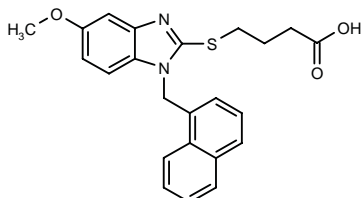
308641

4-[1-(Naphthalen-1-ylmethyl)-1*H*-benzimidazol-2-ylsulfonyl]butyric acid



C22 H20 N2 O2 S; Mol wt: 376.4780

ACTION – Human mast cell chymase inhibitor ($IC_{50} = 1-10$ nM) with good metabolic stability, potentially useful for the treatment of inflammatory, allergic, respiratory, circulatory and bone diseases. Another compound from this series of benzimidazole derivatives is:



308642: C23 H22 N2 O3 S

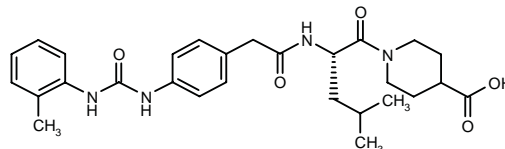
SOURCE – Teijin.

REFERENCES

1. Tsuchiya, N. et al. (Teijin Ltd.) *Human chymase inhibitors*. WO 0153272.

308677

1-[*N*-[2-[4-[3-(2-Methylphenyl)ureido]phenyl]acetyl]-*L*-leucyl]piperidine-4-carboxylic acid



C₂₈ H₃₆ N₄ O₅; Mol wt: 508.6154

ACTION – Integrin, particularly $\alpha_4\beta_1$, $\alpha_4\beta_7$ and/or $\alpha_9\beta_1$ integrin, antagonist and inhibitor of cell adhesion, proven to inhibit the adhesion of Jurkat cells to VCAM-1 *in vitro* ($IC_{50} < 10 \mu M$). It exhibited adequate pharmacokinetic parameters at 10 mg/kg i.p. in mice. Potentially useful in the treatment of atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), allergy, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis and transplant rejection, among other immune, autoimmune and inflammatory disorders.

SOURCE – Bayer.

REFERENCES

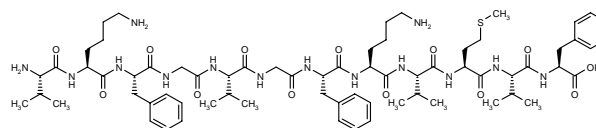
1. Fischer, R. et al. (Bayer AG) *Piperidyl carboxylic acids as integrin antagonists*. DE 10006453, WO 0158871.

CALP2^{1,3,4}

307422

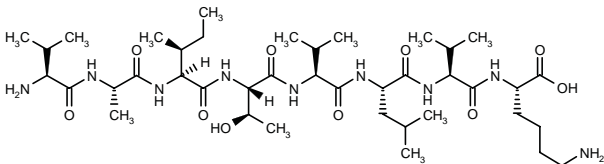
L-Valyl-L-lysyl-L-phenylalanyl-glycyl-L-valyl-glycyl-L-phenylalanyl-L-lysyl-L-valyl-L-methionyl-L-valyl-L-phenylalanine

Calcium-like peptide 2



C68 H104 N14 O13 S: Mol wt: 1357.7210

ACTION – Calcium-like peptide that interacts with calcium-binding EF-hand motifs, regulates calcium channels and inhibits VLA-5 (very late antigen-5)-mediated adhesion of mast cells to fibronectin. The peptide had no effect on airways responsiveness itself. It blocked **CALP1**-induced airways hyperresponsiveness, and opened EF-hand-containing calcium channels, thereby increasing intracellular calcium concentrations in epithelial cells, resulting in increased nitric oxide (NO) production. Potentially useful for the treatment of allergic diseases such as asthma.



CALP1¹⁻⁴ [307413]: C40 H75 N9 O10

SOURCES – University of Alabama at Birmingham, Birmingham, AL (US); Jansen; Utrecht University, Utrecht (NL).

REFERENCES

1. Houtman, R. et al. *Attenuation of very late antigen-5-mediated adhesion of bone marrow-derived mast cells to fibronectin by peptides with inverted hydropathy to EF-hands.* J Immunol 2001, 166(2): 861.

2. Manion, M.K. et al. *A new type of Ca²⁺ channel blocker that targets Ca²⁺ sensors and prevents Ca²⁺-mediated apoptosis.* FASEB J 2000, 14(10): 1297.

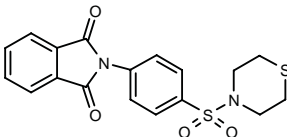
3. Ten Broeke, R. et al. *Calcium sensors as new therapeutic targets for airway hyperresponsiveness and asthma.* FASEB J 2001, 15(10): 1831.

4. Villain, M. et al. *De novo design of peptides targeted to the EF hands of calmodulin.* J Biol Chem 2000, 275(4): 2676.

LASSBio-468^{1,2}

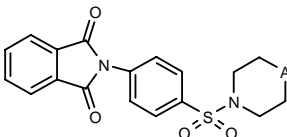
308314

2-[4-(Thiomorpholin-4-ylsulfonyl)phenyl]-2,3-dihydro-1*H*-isindole-1,3-dione



C18 H16 N2 O4 S2; Mol wt: 388.4664

ACTION – Antiinflammatory agent, a thalidomide derivative shown to inhibit phosphodiesterase type 4 (PDE4) and type 5 (PDE5) by 50 and 21%, respectively, at 50 μM. In a murine model of endotoxin-induced lung neutrophil recruitment and TNF-α production, a dose of 10 mg/kg i.p. 45 min prior to lipopolysaccharide significantly reduced neutrophilia (80%) and TNF-α levels (70%). Other related compounds are:



Compound	A	Formula
LASSBio-469 ^{1,2} [308872]	-O-	C ₁₈ H ₁₆ N ₂ O ₅ S
LASSBio-449 ² [308973]	-N(Me)-	C ₁₉ H ₁₉ N ₃ O ₄ S
LASSBio-470 ² [308974]	-N(Ph)-	C ₂₄ H ₂₁ N ₃ O ₄ S
LASSBio-544 ² [308975]	-NH-	C ₁₈ H ₁₇ N ₃ O ₄ S

SOURCES – CNRS; Universidade Federal do Rio de Janeiro, Rio de Janeiro (BR).

REFERENCES

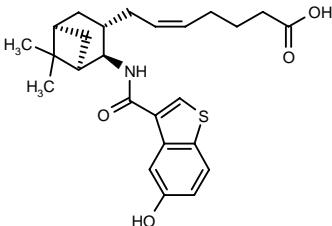
1. Legora, A.M. et al. *Anti-inflammatory effects of thalidomide-derived compounds on LPS-induced inflammation in mouse lung.* Inflamm Res 2001, 50(Suppl. 3): Abst 083.

2. Rasps, M.L. et al. *Design, synthesis and evaluation of the antiinflammatory properties of new phthalimide-piperazine phosphodiesterase inhibitors using molecular hybridization.* 23rd Annu Meet Braz Chem Soc (May 23-26, Poços de Caldas) 2000, Abst.

S-5751*

257050

(1*R*,2*R*,3*S*,5*S*)-7-[2-(5-Hydroxybenzothiophen-3-ylcarboxamido)-6,6-dimethylbicyclo[3.1.1]hept-3-yl]-5(*Z*)-heptenoic acid



C25 H31 N O4 S; Mol wt: 441.5889

ACTION – Potent and selective prostaglandin DP receptor antagonist (K_i = 1.6 nM in human platelets; IC₅₀ = 0.9 nM for functional antagonism in human platelets) with 15-fold selectivity over TP receptors (K_i = 24.2 nM in human platelets). Compound showed little or no activity against IP or EP₂ receptors. In an allergic rhinitis model in ovalbumin-sensitized guinea pigs, oral pretreatment with compound (1-10 mg/kg) significantly inhibited the antigen-induced early-phase nasal response (increase in intranasal pressure, sneezing and plasma exudation in nasal mucosa) and late-phase response (plasma exudation and eosinophil infiltration). In an allergic airways inflammation model in sensitized guinea pigs, compound at a dose of 10 mg/kg p.o. significantly inhibited antigen-induced eosinophilia in bronchoalveolar lavage fluid. Further studies in allergic conjunctivitis in guinea pigs demonstrated that compound (1-10 mg/kg p.o.) strongly suppressed the increase in vascular permeability in the conjunctiva. Compound is undergoing phase II clinical trials in patients with allergic asthma.

SOURCE – Shionogi.

REFERENCES

1. Arimura, A. (Shionogi & Co. Ltd.) *Remedies for itching containing PGD2 antagonists.* EP 1084711, WO 9962555.

2. Honma, T. and Hiramatsu, Y. (Shionogi & Co. Ltd.) *Process for producing 5-hydroxybenzo[b]thiophene-3-carboxylic acid derivs.* EP 1069122, WO 9950260.

3. Honma, T. et al. (Shionogi & Co. Ltd.) *Benzothiophenecarboxamide derivs. and PGD2 antagonists comprising them.* EP 0944614, JP 2000514824, US 6083974, WO 9825919.

4. Honma, T. et al. (Shionogi & Co. Ltd.) *Process for producing benzothiophenecarboxylic acid amide derivs.* EP 1069123, WO 9950261.

5. Ohtani, M. et al. (Shionogi & Co. Ltd.) *Bicyclic amino derivs. and PGD2 antagonist containing the same.* EP 0837052, JP 2001288160, WO 9700853.

6. Arimura, A. et al. *Prevention of allergic inflammation by a novel prostaglandin receptor antagonist, S-5751.* J Pharmacol Exp Ther 2001, 298(2): 411.

7. Tsuru, T. et al. *Bicyclo[2.2.1]heptane and 6,6-dimethylbicyclo[3.1.1]heptane derivatives: Orally active, potent, and selective prostaglandin D2 receptor antagonists.* J Med Chem 1997, 40(22): 3504.

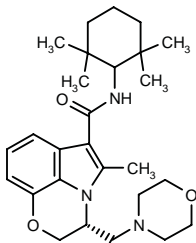
8. Shionogi: *Annual Report 1998.* DailyDrugNews.com (Daily Essentials) 1998, Oct 23.

*Identified compound **257050** Drug Data Rep 1998, 020(03): 0217.

TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY
DISEASES

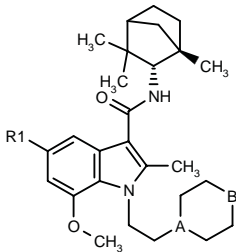
308751

5-Methyl-3(*R*)-(morpholin-4-ylmethyl)-*N*-(2,2,6,6-tetramethylcyclohexyl)-2,3-dihydro[1,4]oxazino[2,3,4-*h*]-indole-6-carboxamide

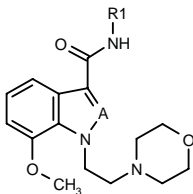


C27 H39 N3 O3; Mol wt: 453.6231

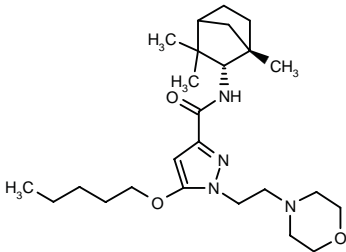
ACTION – Cannabinoid receptor modulator, potentially useful for the treatment of respiratory diseases such as chronic obstructive pulmonary disease (COPD), emphysema, asthma and bronchitis, as well as transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, graft-versus-host disease, psoriasis, cancer, allergic rhinitis and ischemia/reperfusion injury. Other specifically claimed compounds from this series of pyrrole, pyrazole and imidazole derivatives include the following:



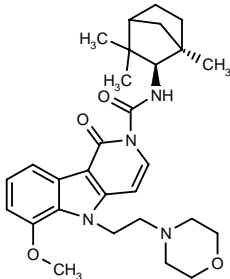
Compound	R1	A	B	Formula
308755	F	N	O	C ₂₇ H ₃₈ FN ₃ O ₃
308756	H	CH	NH	C ₂₈ H ₄₁ N ₃ O ₂



Compound	R1	A	Formula
308762	1-(PhCH2)-3(S)-pyrrolidinyl	N	C ₂₈ H ₃₃ N ₅ O ₃
308763	(S)-CH(<i>t</i> -Bu)CO ₂ Me	C(Me)	C ₂₄ H ₃₅ N ₃ O ₅
308765	(S)-CH(CH ₂ Ph)CO ₂ Me	CH	C ₂₆ H ₃₁ N ₃ O ₅



308757: C25 H42 N4 O3



308760: C29 H38 N4 O4

SOURCE – Bristol-Myers Squibb.

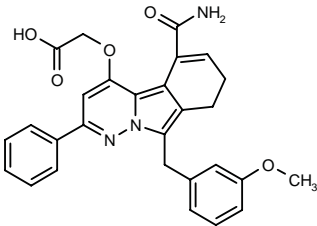
REFERENCES

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AGENTS FOR RESPIRATORY
DISTRESS SYNDROME

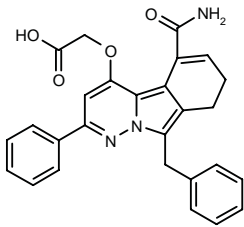
305451

2-[5-Carbamoyl-9-(3-methoxybenzyl)-2-phenyl-7,8-dihydropyridazino[6,1-*a*]isoindol-4-yloxy]acetic acid



C28 H25 N3 O5; Mol wt: 483.5215

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor with selectivity for sPLA₂ type V (IC₅₀ = 0.0002, 0.049, 0.006 and 0.002 μM, respectively, against human recombinant enzyme type V, I, II and X), with potential for the treatment of a broad range of disorders including septic shock, adult respiratory distress syndrome (ARDS), pancreatitis, bronchial asthma, allergic rhinitis, rheumatoid arthritis, arteriosclerosis, stroke, cerebral infarction, ulcerative colitis, psoriasis, heart failure and myocardial infarction. Another exemplified compound from this series of tricyclic azaindolizine derivatives is:



305452: C27 H23 N3 O4

SOURCE – Shionogi.

REFERENCES

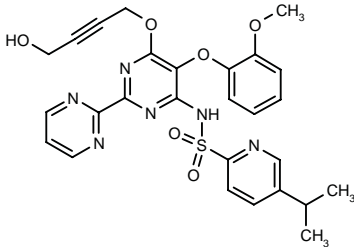
1. Fuji, M. et al. (Shionogi & Co. Ltd.) *Tricyclic azaindolizine derivs. having an sPLA2-inhibiting effect.* WO 0136420.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

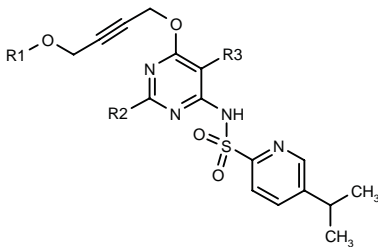
307618

N-[6-(4-Hydroxy-2-butynyloxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]-5-isopropylpyridine-2-sulfonamide



C27 H26 N6 O6 S; Mol wt: 562.6044

ACTION – Selective endothelin ET_A receptor antagonist, as demonstrated in binding assays by IC₅₀ values of 53 and 2030 nM, respectively, for human ET_A and ET_B receptors cloned in CHO cells, as well as in functional assays, where it exhibited pA₂ values of 7.15 and 5.89, respectively, against endothelin-induced contractions of isolated rat aortic rings (ET_A) and rat tracheal rings (ET_B). Potentially useful for the treatment of hypertension, coronary disease, cardiac insufficiency, ischemia and renal failure. Other exemplified compounds from this series of butyne diol derivatives include the following:



Compound	R1	R2	R3	Formula
307619	H	4-morpholinyl	2-MeO-PhO	C ₂₇ H ₃₁ N ₆ O ₇ S
307620	H	4-Pyr	4-Me-Ph	C ₂₈ H ₂₇ N ₅ O ₄ S
307621	2-Pyr-NHCO	4-Pyr	2-MeO-PhO	C ₃₄ H ₃₁ N ₇ O ₇ S

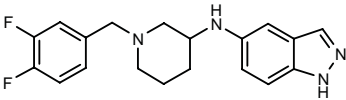
SOURCE – Actelion.

REFERENCES

1. Bolli, M. et al. (Actelion Ltd.) *Butyne diol derivs.* WO 0146156.

308603

N-[1-(3,4-Difluorobenzyl)piperidin-3-yl]-1*H*-indazol-5-amine



C19 H20 F2 N4; Mol wt: 342.3910

ACTION – A representative compound from a series of nitrogenated heterocyclic Rho kinase inhibitors with potential for the treatment of a broad range of disorders such as hypertension, asthma, angina pectoris, cerebrovascular spasm, peripheral circulatory disorders, glaucoma, cancer, arteriosclerosis, inflammation, autoimmune diseases, osteoporosis, nephritis, thrombo-embolic disorders and fibrosis. *In vitro*, compound was shown to inhibit MCP-1-stimulated migration of human-derived histiocytic lymphoma U-937 cells expressing murine CCR2 (U-937/CCR2), giving 81.9 ± 11.9% inhibition at 0.3 µM. *In vivo*, it was shown to significantly improve proteinuria in a rat model of anti-GBM antibody-induced nephritis at 30 mg/kg b.i.d. p.o. x 2 weeks, as well as to lower blood pressure in spontaneously hypertensive rats (24.1 ± 3.8% decrease at 30 mg/kg p.o.).

SOURCE – Kirin Brewery.

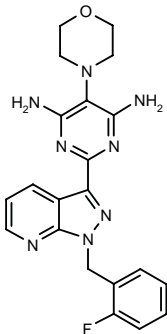
REFERENCES

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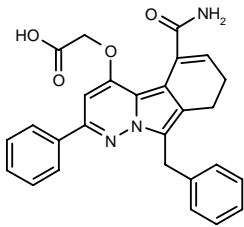
BAY-41-8543^{*,1-3}

285900

2-[1-(2-Fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-(4-morpholinyl)pyrimidine-4,6-diamine



C21 H21 F N8 O; Mol wt: 420.4499



305452: C27 H23 N3 O4

SOURCE – Shionogi.

REFERENCES

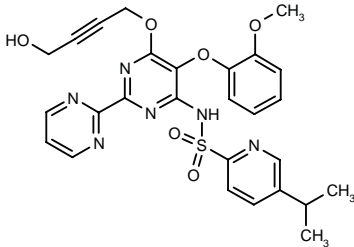
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

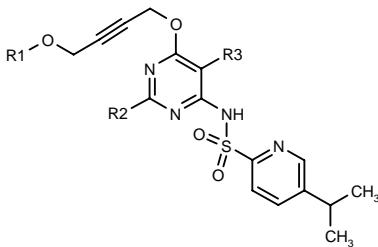
307618

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ACTION – Selective endothelin ET_A receptor antagonist, as demonstrated in binding assays by IC₅₀ values of 53 and 2030 nM, respectively, for human ET_A and ET_B receptors cloned in CHO cells, as well as in functional assays, where it exhibited pA₂ values of 7.15 and 5.89, respectively, against endothelin-induced contractions of isolated rat aortic rings (ET_A) and rat tracheal rings (ET_B). Potentially useful for the treatment of hypertension, coronary disease, cardiac insufficiency, ischemia and renal failure. Other exemplified compounds from this series of butyne diol derivatives include the following:



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307620	H	4-Pyr	4-Me-Ph	C ₂₈ H ₂₇ N ₅ O ₄ S
307621	2-Pyr-NHCO	4-Pyr	2-MeO-PhO	C ₃₄ H ₃₁ N ₇ O ₇ S

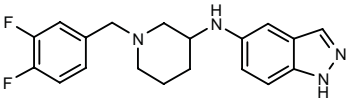
SOURCE – Actelion.

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C19 H20 F2 N4; Mol wt: 342.3910

ACTION – A representative compound from a series of nitrogenated heterocyclic Rho kinase inhibitors with potential for the treatment of a broad range of disorders such as hypertension, asthma, angina pectoris, cerebrovascular spasm, peripheral circulatory disorders, glaucoma, cancer, arteriosclerosis, inflammation, autoimmune diseases, osteoporosis, nephritis, thrombo-embolic disorders and fibrosis. *In vitro*, compound was shown to inhibit MCP-1-stimulated migration of human-derived histiocytic lymphoma U-937 cells expressing murine CCR2 (U-937/CCR2), giving 81.9 ± 11.9% inhibition at 0.3 µM. *In vivo*, it was shown to significantly improve proteinuria in a rat model of anti-GBM antibody-induced nephritis at 30 mg/kg b.i.d. p.o. x 2 weeks, as well as to lower blood pressure in spontaneously hypertensive rats (24.1 ± 3.8% decrease at 30 mg/kg p.o.).

SOURCE – Kirin Brewery.

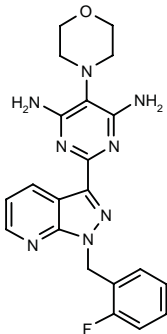
REFERENCES

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BAY-41-8543^{*,1-3}

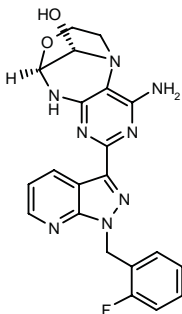
285900

2-[1-(2-Fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-(4-morpholinyl)pyrimidine-4,6-diamine



C21 H21 F N8 O; Mol wt: 420.4499

ACTION – Nitric oxide (NO)-independent stimulator of soluble guanylate cyclase (sGC) proven to relax phenylephrine-precontracted rabbit aortic rings ($IC_{50} = 0.2 \mu M$) and to stimulate isolated recombinant sGC alone and in the presence of NO. *In vivo* in rats, compound (0.1-1 mg/kg p.o.) produced strong, dose-dependent and long-lasting (> 2 h) reductions in blood pressure. The major metabolite of compound (**307752**) isolated in rats and dogs showed strong sGC-activating and blood pressure-lowering effects. Potentially useful for the treatment of hypertension, coronary heart disease and congestive heart failure.



307752³: C₂₁ H₁₉ F N₈ O₂

SOURCE – Bayer.

REFERENCES

1. Straub, A. et al. (Bayer AG) *Substd. pyrazolo derivs. condensed with six-membered heterocyclic rings*. DE 19834044, EP 1102768, WO 0006569.

2. Feurer, A. et al. *3-(2-Pyrimidinyl)pyrazolo[3,4-b]pyridines: A novel class of orally active NO-independent stimulators of soluble guanylate cyclase*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 205.

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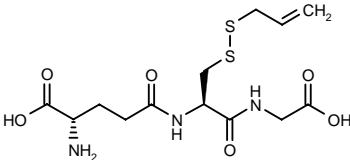
³Identified compound **285900** Drug Data Rep 2000, 022(05): 0426.

TREATMENT OF DISORDERS OF
THE CORONARY ARTERIES
AND ATHEROSCLEROSIS

305460

S-(Allylsulfanyl)glutathione

L-γ-Glutamyl-S-(allylsulfanyl)-L-cysteinyglycine



C₁₃ H₂₁ N₃ O₆ S₂; Mol wt: 379.4559

ACTION – Agent for the treatment of atherosclerosis, coronary artery disease, thrombosis, hypercholesterolemia and hyperlipidemia, hypertension, Alzheimer's disease, glaucoma, cancer and inflammatory disorders, as well as for weight control, obtained by reaction of glutathione with allicin, the main active substance of fresh garlic extract. Compound exhibits SH-modifying and antioxidant properties, as demonstrated by inhibition of SH-protease papain activity at 2.0-9.0 mM, as well as in several tests measuring lipid peroxide or hydroxyl radical production. In addition, it was shown to inhibit the proliferation of human breast cancer MCF-7 cells, with about 50% inhibition being observed at a concentration of 32 μM .

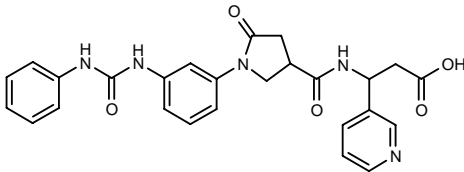
SOURCE – Yeda.

REFERENCES

1. Miron, T. et al. (Yeda Research & Development Co. Ltd.) *S-Allylmercaptogluthathione and uses thereof*. WO 0136450.

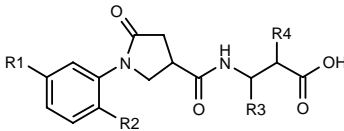
307143

3-[5-Oxo-1-[3-(3-phenylureido)phenyl]pyrrolidin-3-yl-carboxamido]-3-(3-pyridyl)propionic acid



C₂₆ H₂₅ N₅ O₅; Mol wt: 487.5135

ACTION – Integrin antagonist claimed for the treatment of diseases modulated by integrin receptors such as $\alpha_v\beta_3$, $\alpha_v\beta_5$ or $\alpha_v\beta_6$ receptors, particularly atherosclerosis, restenosis, inflammation, wound healing, cancer, metastasis, bone resorption disorders, diabetic retinopathy, macular degeneration, angiogenesis or viral infections. Other exemplified 1-(aminophenyl)-2-pyrrolidinones are:



Compound	R1	R2	R3	R4	Formula
307144	4,5-dihydro-1H-imidazol-2-yl-NH	H	3-Pyr	H	C ₂₂ H ₂₄ N ₆ O ₄
307145	NHCONHCH ₂ Ph	OMe	3-Pyr	H	C ₂₈ H ₂₉ N ₅ O ₆
307146	2-thienyl-CH ₂ NHCOCH ₂	H	3-Pyr	H	C ₂₆ H ₂₆ N ₄ O ₅ S
307147	2-Pyr-NHCH ₂	H	H	NHSO ₂ Ph	C ₂₆ H ₂₇ N ₅ O ₆ S
307148	NHCONHCH ₂ Ph	H	3-thienyl	H	C ₂₆ H ₂₆ N ₄ O ₅ S
307149	2-F-PhCH ₂ NHCONH	H	3-Pyr	H	C ₂₇ H ₂₆ FN ₅ O ₅
307150	2-CF ₃ -Ph-CH ₂ NHCONH	H	3-Pyr	H	C ₂₈ H ₂₆ F ₃ N ₅ O ₅

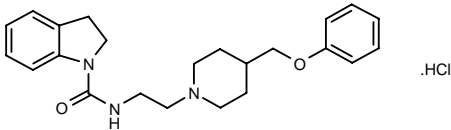
SOURCE – Amgen.

REFERENCES

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307441

N-[2-[4-(Phenoxymethyl)piperidin-1-yl]ethyl]indoline-1-carboxamide hydrochloride



C23 H29 N3 O2 . HCl; Mol wt: 415.9620

ACTION – Agent for the treatment or prevention of disorders involving endothelial dysfunction such as atherosclerosis, myocardial and peripheral ischemia, cardiac insufficiency and pulmonary arterial hypertension, as well as for the prevention of vascular complications, for example after cardiac transplantation, that acts by blocking the decrease in nitric oxide (NO) availability induced by both inhibition of endothelial nitric oxide synthase (eNOS) and by superoxide anion-induced oxidative stress. Its activity was demonstrated in *in vitro* assays, where it inhibited the endothelial dysfunction induced by the NOS inhibitor LNA in rat thoracic aorta rings (8, 26 and 29% inhibition, respectively, at 0.01, 0.03 and 0.1 μ M), as well as that induced by xanthine oxidase–hypoxanthine in rabbit aortic rings (17% inhibition at 0.03 μ M). In addition, it was shown to increase cGMP production stimulated by acetylcholine in the presence of LNA in rat aortic rings by 28.1% at 0.1 μ M.

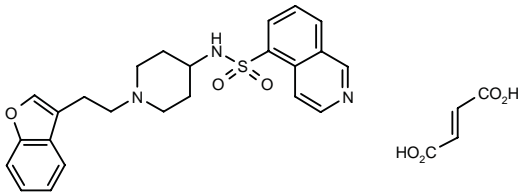
SOURCE – ADIR.

REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) Linear or cyclic ureas, a process for their preparation and pharmaceutical compsns. containing them. EP 1113014, FR 2803298, JP 2001187782.

308080

N-[1-[2-(1-Benzofuran-3-yl)ethyl]piperidin-4-yl]isoquinoline-5-sulfonamide fumarate



C24 H25 N3 O3 S . C4 H4 O4; Mol wt: 551.6171

ACTION – Agent for the treatment of disorders involving endothelial dysfunction that acts by blocking the decrease in nitric oxide (NO) availability induced by endothelial nitric oxide synthase (eNOS) inhibition or by superoxide anion-related oxidative stress. At 3 nM, it inhibited endothelial dysfunction induced by the eNOS inhibitor LNA in rat aortic rings by 23%, and that induced by superoxide anion in rabbit aortic rings by 28.3%. In rat aortic rings, it was shown to increase acetylcholine-induced cGMP production in the presence of LNA by 142.7% at the same concentration. Potential uses of this compound include atherosclerosis, myocardial and peripheral ischemia, cardiac insufficiency, pulmonary arterial hypertension and vascular complications, for example after cardiac transplantation.

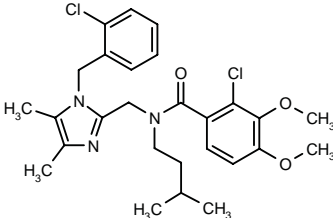
SOURCE – ADIR.

REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) 4-Sulfonamide piperidine derivs., method for their preparation and pharmaceutical compsns. containing them. EP 1122254, FR 2804429, JP 2001233874.

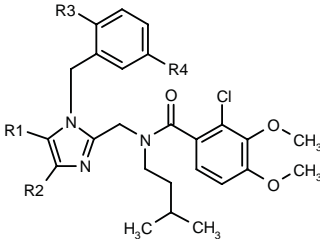
308174

2-Chloro-N-[1-(2-chlorobenzyl)-4,5-dimethyl-1 H-imidazol-2-ylmethyl]-3,4-dimethoxy-N-(3-methylbutyl)benzamide



C27 H33 Cl2 N3 O3; Mol wt: 518.4817

ACTION – A selective modulator of bradykinin B₂ receptors with potential utility in the treatment of renal diseases, heart failure, hypertension, Ménière’s disease, vaginal inflammation and pain, peripheral circulatory disorders, climacteric disturbances, myocardial ischemia and infarction, angina pectoris, restenosis following PTCA, hepatitis, liver cirrhosis, pancreatitis, diabetes and complications thereof, male infertility, glaucoma, asthma, rhinitis, and for increasing blood–brain barrier permeability. Other exemplified substituted imidazole derivatives are:



Compound	R1	R2	R3	R4	Formula
308175	Me	Me	OH	H	C ₂₇ H ₃₄ ClN ₃ O ₄
308176	Me	Me	OCH ₂ CN	H	C ₂₉ H ₃₅ ClN ₄ O ₄
308177	Cl	Cl	Cl	H	C ₂₈ H ₂₇ Cl ₄ N ₃ O ₃
308178	Me	Me	OH	Br	C ₂₇ H ₃₃ BrClN ₃ O ₄
308179	Me	Me	SO ₂ NH ₂	H	C ₂₇ H ₃₅ ClN ₄ O ₃ S
308180	Cl	Cl	5-tetrazolyl	H	C ₂₆ H ₂₆ Cl ₃ N ₇ O ₃

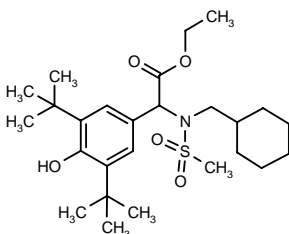
SOURCE – Neurogen.

REFERENCES

1. Rachwal, S. et al. (Neurogen Corp.) *Subst. imidazoles as selective modulators of bradykinin B2 receptors*. WO 0156995.

308552

2-[*N*-(Cyclohexylmethyl)-*N*-(methylsulfonyl)amino]-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester



C26 H43 N O5 S; Mol wt: 481.6937

ACTION – A sulfonamide-containing compound with the ability to lower lipoprotein(a) (Lp[a]) levels, as demonstrated by IC₅₀ values of 1.92 and 27.25 μM in the LPABC and LPA3 tests, respectively. Potentially useful for the treatment of atherosclerosis, coronary heart disease and restenosis.

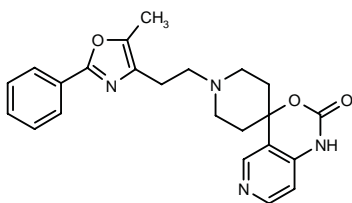
SOURCE – Pfizer.

REFERENCES

1. Lee, H.T. et al. (Pfizer Inc.) *Sulfonamide cpds. and methods of treating atherosclerosis and restenosis*. US 6284795.

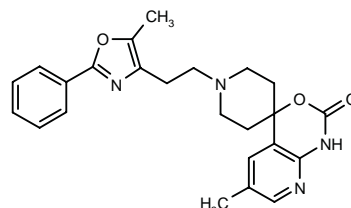
308608

1-[2-(5-Methyl-2-phenyloxazol-4-yl)ethyl]spiro[piperidine-4,4'-pyrido[4,3-*d*][1,3]oxazin]-2'-(1'*H*)-one

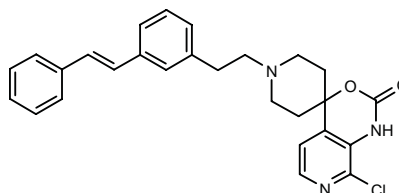


C23 H24 N4 O3; Mol wt: 404.4676

ACTION – Potent and selective chemokine MCP-1 antagonist (IC₅₀ = 0.2 μg/ml) with at least 30-fold selectivity over α₁-adrenoceptors. Potentially useful for the prevention and treatment of chronic inflammatory diseases including arteriosclerosis, pulmonary hypertension, rheumatism, asthma and kidney diseases. Other exemplified pyridoxazine derivatives are:



308609: C24 H26 N4 O3



308610: C27 H26 Cl N3 O2

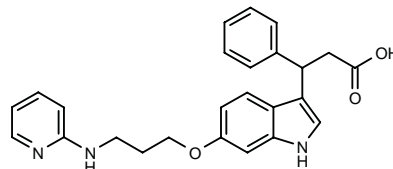
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Horino, H. et al. (Daiichi Pharmaceutical Co., Ltd.) *Pyridoxazine derivs*. WO 0157044.

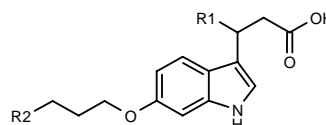
308742

3-Phenyl-3-[6-[3-(pyridin-2-ylamino)propoxy]-1*H*-indol-3-yl]propionic acid



C25 H25 N3 O3; Mol wt: 415.4905

ACTION – Integrin, particularly α_vβ₃ (vitronectin receptor), antagonist useful for the treatment or prevention of thrombosis, cardiovascular disorders, atherosclerosis, inflammation, restenosis, rheumatoid arthritis, macular degenerative disorders, diabetic retinopathy, cancer, osteoporosis and infections. Other exemplified compounds from this series of indol-3-yl derivatives include the following:



Compound	R1	R2	Formula
308743	Ph	2-imidazolyl-NH	C ₂₃ H ₂₄ N ₄ O ₃
308744	Ph	2-Pyr-NHCH ₂	C ₂₆ H ₂₇ N ₃ O ₃
308745	4-F-Ph	2-Pyr-NH	C ₂₆ H ₂₄ FN ₃ O ₃
308746	2,1,3-benzo-thiadiazol-5-yl	4,5-dihydro-1H-imidazol-2-yl-NH	C ₂₃ H ₂₄ N ₆ O ₃ S
308747	Ph	4-oxo-4,5-dihydro-1H-imidazol-2-yl-NH	C ₂₃ H ₂₄ N ₄ O ₄
308749	Ph	NHC(=N-CN)NHMe	C ₂₃ H ₂₅ N ₅ O ₃
308750	(S)-Ph	2-Pyr-NH	C ₂₆ H ₂₅ N ₃ O ₃

SOURCE – Merck KGaA.

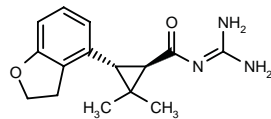
REFERENCES

1. Goodman, S. et al. (Merck Patent GmbH) *Indol-3-yl derivs.* DE 10006139, WO 0158893.

BMS-284640

308012

(1*R*,3*R*)-*N*-(Diaminomethylene)-3-(2,3-dihydro-1-benzofuran-4-yl)-2,2-dimethylcyclopropanecarboxamide



C15 H19 N3 O2; Mol wt: 273.3341

ACTION – Potent and selective inhibitor of the Na⁺/H⁺ exchanger (NHE) with improved potency for NHE-1 and selectivity over the NHE-2 isoform compared to cariporide and eniporide (IC₅₀ = 0.009, 3.4 and 0.38 μM, respectively, against NHE-1; IC₅₀ = 1.8, 62 and 17 μM, respectively, against NHE-2). Compound exhibited a good pharmacokinetic profile in rats, with 63% oral availability and a moderate plasma half-life (3 h). Selected for further development.

SOURCE – Bristol-Myers Squibb.

REFERENCES

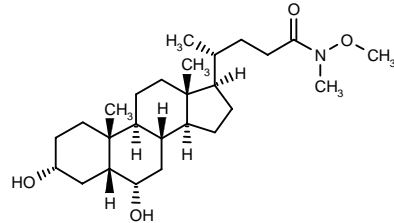
1. Ahmad, S. et al. (Bristol-Myers Squibb Co.) *Acyl guanidine sodium/proton exchange inhibitors and method.* EP 1041980, US 6011059, WO 9933460.

2. Ahmad, S. et al. *Arylcyclopropanecarboxyl guanidines as novel, potent, and selective inhibitors of the sodium hydrogen exchanger isoform-1.* J Med Chem 2001, 44(20): 3302.

HYPOCHOLAMIDE

308658

3α,6α-Dihydroxy-*N*-methoxy-*N*-methyl-5β-cholan-24-amide



C26 H45 NO4 ; Mol wt: 435.6445

ACTION – Bile acid analogue able to selectively activate the liver X receptor LXRα (EC₅₀ = 0.2 μM), and to a lesser extent UR receptors (EC₅₀ = 1 μM), it was inactive at the farnesoid X receptor (FXR) at concentrations up to 20 μM. *In vivo*, compound exhibited hypolipidemic effects in hypercholesterolemic rats, mice and hamsters and showed a unique pharmacokinetic profile, with a long serum half-life of 6 days in hamsters and mainly renal excretion (90%). Potentially useful for the treatment or prevention of atherosclerosis.

SOURCE – University of Chicago, Chicago, IL (US).

REFERENCES

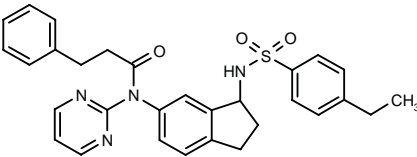
1. Song, C. and Liao, S.S. *Hypolipidemic effects of selective liver X receptor alpha agonists.* Steroids 2001, 66(9): 673.

2. Song, C. et al. *Effect of a selective liver X receptor agonist on atherosclerosis progression and regression of apoE knock-out mice.* Circulation 2001, 104(17, Suppl. 2): Abst 1586.

ANTIARRHYTHMIC DRUGS

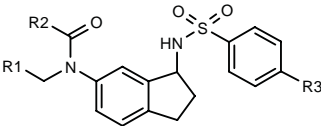
307622

N-[3-(4-Ethylphenylsulfonamido)-2,3-dihydro-1*H*-inden-5-yl]-3-phenyl-*N*-(2-pyrimidinyl)propionamide



C30 H30 N4 O3 S; Mol wt: 526.6580

ACTION – Agent for the treatment of cardiac arrhythmias and cell proliferative disorders, an inhibitor of voltage-dependent potassium channel, particularly Kv1.5 and Kv1.3 channel, function, as demonstrated by 66% inhibition of potassium currents in CHO cells stably expressing the Kv1.5 potassium channel at 0.1 μM. Other exemplified bicyclic compounds include the following:



Compound	R1	R2	R3	Formula
307623	3-Pyr	CH2CH2Ph	Et	C ₃₂ H ₃₃ N ₃ O ₃ S
307624	6-Me-2-Pyr	CH2CH2Ph	Et	C ₃₃ H ₃₅ N ₃ O ₃ S
307625	1-Me-2-imidazolyl	CH2CH2Ph	Et	C ₃₁ H ₃₄ N ₄ O ₃ S
307626	6-Me-2-Pyr	2-Ph-cyclopropyl	Et	C ₃₄ H ₃₅ N ₃ O ₃ S
307628	1-Me-2-imidazolyl	3-Cl-Ph	Et	C ₂₉ H ₂₉ ClN ₄ O ₃ S
307630	6-Me-2-Pyr	2-Ph-cyclopropyl	F	C ₃₂ H ₃₀ FN ₃ O ₃ S
307633	1-Me-2-imidazolyl	2-Ph-cyclopropyl	F	C ₃₀ H ₂₉ FN ₄ O ₃ S

SOURCE – ICAGEN.

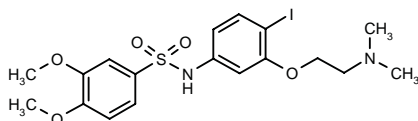
REFERENCES

1. Gross, M. et al. (ICAGEN, Inc.) *Potassium channel inhibitors.* WO 0146155.

HEART FAILURE THERAPY

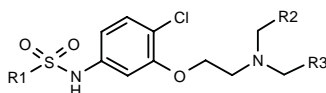
307712

N-[3-[2-(Dimethylamino)ethoxy]-4-iodophenyl]-3,4-dimethoxybenzenesulfonamide



C18 H23 I N2 O5 S; Mol wt: 506.3547

ACTION – Urotensin-II receptor antagonist with potential for the treatment of conditions associated with urotensin-II imbalance such as congestive heart failure, stroke, ischemic heart disease, angina, myocardial ischemia, cardiac arrhythmias, essential and pulmonary hypertension, chronic obstructive pulmonary disease (COPD), restenosis, asthma, neurogenic inflammation, metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function disorders and diabetes. Other specifically claimed compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2=R3	Formula
307713	3-Cl-4-F-Ph	H	C ₁₆ H ₁₇ Cl ₂ FN ₂ O ₃ S
307714	4-Cl-2-Naph	H	C ₂₀ H ₂₀ Cl ₂ N ₂ O ₃ S
307715	5-Cl-1-Naph	H	C ₂₀ H ₂₀ Cl ₂ N ₂ O ₃ S
307716	2-Me-4,5-(MeO)2-Ph	H	C ₁₉ H ₂₅ ClN ₂ O ₅ S
307717	4-Br-2,6-(Me)2-Ph	Me	C ₁₈ H ₂₂ BrClN ₂ O ₃ S
307718	2-Cl-4,5-(MeO)2-Ph	H	C ₁₈ H ₂₂ Cl ₂ N ₂ O ₅ S

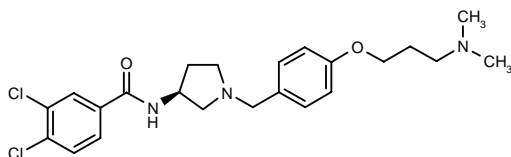
SOURCE – GlaxoSmithKline.

REFERENCES

1. Dhanak, D. and Knight, S.D. (SmithKline Beecham Corp.) *Urotensin-II receptor antagonists*. WO 0145694.

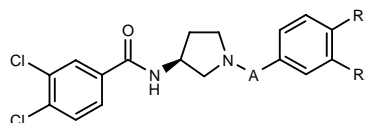
307719

3,4-Dichloro-*N*-[1-[4-[3-(dimethylamino)propoxy]benzyl]pyrrolidin-3(*S*)-yl]benzamide

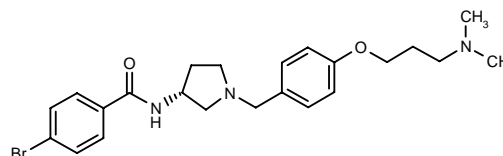


C23 H29 Cl2 N3 O2; Mol wt: 450.4071

ACTION – Urotensin-II receptor antagonist with potential for the treatment of conditions associated with urotensin-II imbalance, such as congestive heart failure, stroke, ischemic heart disease, angina, myocardial ischemia, cardiac arrhythmias, essential and pulmonary hypertension, chronic obstructive pulmonary disease (COPD), restenosis, asthma, neurogenic inflammation, metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function disorders and diabetes. Other specifically claimed compounds from this series of pyrrolyl and pyridyl derivatives include the following:



Compound	R1	R2	A	Formula
307720	1-Me-3-pyrrolidinyl-O	Br	-CH2-	C ₂₃ H ₂₆ BrCl ₂ N ₃ O ₂
307722	4-Pip-O	Br	-CH2-	C ₂₃ H ₂₆ BrCl ₂ N ₃ O ₂
307723	H	4-Pip-O	-(CH2)2-	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂
307724	3(R)-pyrrolidinyl-O	NO2	-(CH2)2-	C ₂₃ H ₂₆ Cl ₂ N ₄ O ₄
307725	3(R)-pyrrolidinyl-O	Cl	-(CH2)2-	C ₂₃ H ₂₆ Cl ₃ N ₃ O ₂



307721: C23 H30 Br N3 O2

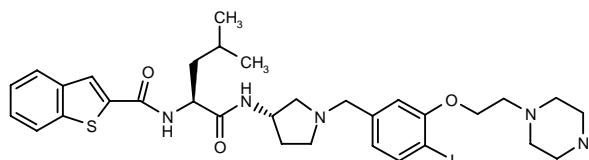
SOURCE – GlaxoSmithKline.

REFERENCES

1. Dhanak, D. et al. (SmithKline Beecham Corp.) *Urotensin-II receptor antagonists*. WO 0145711.

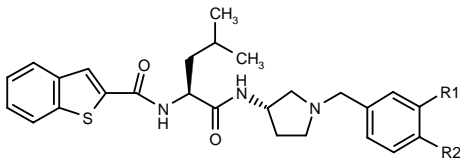
307726

*N*²-(1-Benzothien-2-ylcarbonyl)-*N*¹-[1-[4-iodo-3-[2-(1-piperazinyl)ethoxy]benzyl]pyrrolidin-3(*S*)-yl]-*L*-leucinamide



C32 H42 I N5 O3 S; Mol wt: 703.6818

ACTION – Urotensin-II receptor antagonist with potential for the treatment of conditions associated with urotensin-II imbalance such as congestive heart failure, stroke, ischemic heart disease, angina, myocardial ischemia, cardiac arrhythmias, essential and pulmonary hypertension, chronic obstructive pulmonary disease (COPD), restenosis, asthma, neurogenic inflammation, metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function disorders and diabetes. Other specifically claimed compounds from this series of pyrrolidine derivatives include the following:



Compound	R1	R2	Formula
307727	O(CH2)3N(Me)2	I	C ₃₁ H ₄₁ IN ₄ O ₃ S
307728	H	O(CH2)3N(Me)2	C ₃₁ H ₄₂ N ₄ O ₃ S
307729	Br	O(CH2)3N(Me)2	C ₃₁ H ₄₁ BrN ₄ O ₃ S
307730	Br	1-(PhCH2)-4-Pip-O	C ₃₈ H ₄₅ BrN ₄ O ₃ S
307731	Br	4-Pip-O	C ₃₁ H ₃₉ BrN ₄ O ₃ S

SOURCE – GlaxoSmithKline.

REFERENCES

1. Dhanak, D. et al. (SmithKline Beecham Corp.) *Urotensin-II receptor antagonists*. WO 0145700.

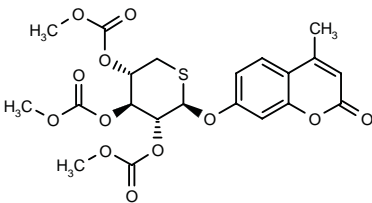
AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

305459

4-Methyl-2-oxo-2H-1-benzopyran-7-yl 2,3,4-tris-O-(methoxycarbonyl)-5-thio-β-D-xylopyranoside

4-Methyl-7-[2,3,4-tris-O-(methoxycarbonyl)-5-thio-β-D-xylopyranosyloxy]-2H-1-benzopyran-2-one



C21 H22 O12 S; Mol wt: 498.4588

ACTION – Antithrombotic agent, a specifically claimed compound from a series of derivatives of 4-methyl-2-oxo-2H-1-benzopyran-7-yl-5-thio-β-D-xylopyranoside that exhibit comparable antithrombotic activity to the parent compound when administered orally; the compounds also show improved solubility and are therefore suitable for i.v. administration. *In vivo*, compound was shown to inhibit venous thrombosis elicited by factor Xa in rats, showing 84% inhibition at 2 h after administration of 5 mg/kg i.v. and 87 and 66% inhibition, respectively, at 4 and 8 h after administration of 9 mg/kg p.o.

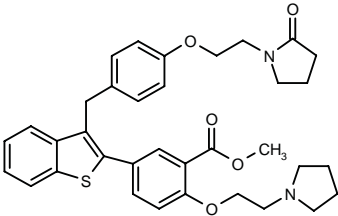
SOURCE – Fournier.

REFERENCES

1. Barberousse, V. et al. (Fournier Industrie et Santé) *β-D-5-Thioxylase derivs., preparation method and therapeutic use*. FR 2801055, WO 0136437.

305461

5-[3-[4-[2-(2-Oxopyrrolidin-1-yl)ethoxy]benzyl]-1-benzothien-2-yl]-2-[2-(1-pyrrolidiny)ethoxy]benzoic acid methyl ester



C35 H38 N2 O5 S; Mol wt: 598.7602

ACTION – Anticoagulant, a specifically claimed compound from a series of benzo[b]thiophene derivatives that exhibit selective thrombin-inhibitory activity and are reported to have an improved pharmacokinetic profile compared to structurally related compounds.

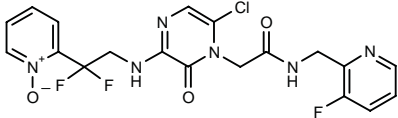
SOURCE – Lilly.

REFERENCES

1. McCowan, J.R. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 0136414.

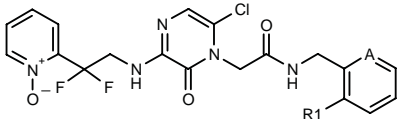
305589

2-[6-Chloro-3-[2,2-difluoro-2-(1-oxidopyridin-2-yl)ethyl-amino]-2-oxo-1,2-dihydropyrazin-1-yl]-N-(3-fluoropyridin-2-ylmethyl)acetamide



C19 H16 Cl F3 N6 O3; Mol wt: 468.8214

ACTION – Antithrombotic agent with thrombin-inhibitory activity, a representative compound from a series of pyrazinone derivatives. Other specifically claimed compounds include the following:

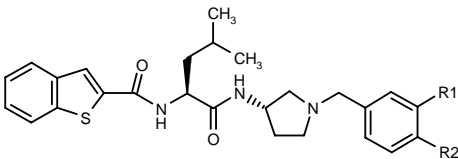


Compound	R1	A	Formula
305930	F	CH	C ₂₀ H ₁₇ ClF ₃ N ₅ O ₃
305932	H	CH	C ₂₀ H ₁₈ ClF ₂ N ₅ O ₃
305933	Cl	N	C ₁₉ H ₁₆ Cl ₂ F ₂ N ₆ O ₃

SOURCE – Merck & Co.

REFERENCES

1. Burgey, C. et al. (Merck & Co., Inc.) *Pyrazinone thrombin inhibitors*. WO 0138323.



Compound	R1	R2	Formula
307727	O(CH2)3N(Me)2	I	C ₃₁ H ₄₁ IN ₄ O ₃ S
307728	H	O(CH2)3N(Me)2	C ₃₁ H ₄₂ N ₄ O ₃ S
307729	Br	O(CH2)3N(Me)2	C ₃₁ H ₄₁ BrN ₄ O ₃ S
307730	Br	1-(PhCH2)-4-Pip-O	C ₃₈ H ₄₅ BrN ₄ O ₃ S
307731	Br	4-Pip-O	C ₃₁ H ₃₉ BrN ₄ O ₃ S

SOURCE – GlaxoSmithKline.

REFERENCES

1. Dhanak, D. et al. (SmithKline Beecham Corp.) *Urotensin-II receptor antagonists*. WO 0145700.

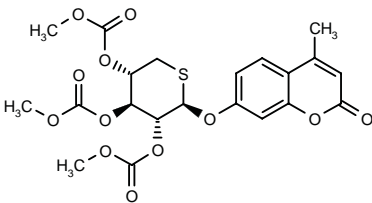
AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

305459

4-Methyl-2-oxo-2H-1-benzopyran-7-yl 2,3,4-tris-O-(methoxycarbonyl)-5-thio-β-D-xylopyranoside

4-Methyl-7-[2,3,4-tris-O-(methoxycarbonyl)-5-thio-β-D-xylopyranosyloxy]-2H-1-benzopyran-2-one



C21 H22 O12 S; Mol wt: 498.4588

ACTION – Antithrombotic agent, a specifically claimed compound from a series of derivatives of 4-methyl-2-oxo-2H-1-benzopyran-7-yl-5-thio-β-D-xylopyranoside that exhibit comparable antithrombotic activity to the parent compound when administered orally; the compounds also show improved solubility and are therefore suitable for i.v. administration. *In vivo*, compound was shown to inhibit venous thrombosis elicited by factor Xa in rats, showing 84% inhibition at 2 h after administration of 5 mg/kg i.v. and 87 and 66% inhibition, respectively, at 4 and 8 h after administration of 9 mg/kg p.o.

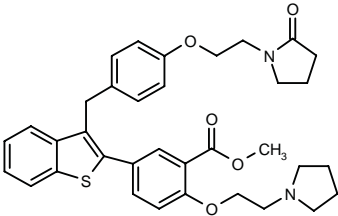
SOURCE – Fournier.

REFERENCES

1. Barberousse, V. et al. (Fournier Industrie et Santé) *β-D-5-Thioxylase derivs., preparation method and therapeutic use*. FR 2801055, WO 0136437.

305461

5-[3-[4-[2-(2-Oxopyrrolidin-1-yl)ethoxy]benzyl]-1-benzothien-2-yl]-2-[2-(1-pyrrolidiny)ethoxy]benzoic acid methyl ester



C35 H38 N2 O5 S; Mol wt: 598.7602

ACTION – Anticoagulant, a specifically claimed compound from a series of benzo[b]thiophene derivatives that exhibit selective thrombin-inhibitory activity and are reported to have an improved pharmacokinetic profile compared to structurally related compounds.

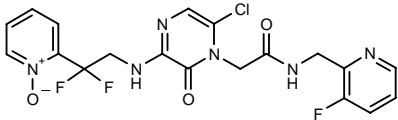
SOURCE – Lilly.

REFERENCES

1. McCowan, J.R. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 0136414.

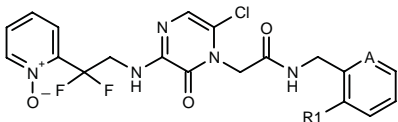
305589

2-[6-Chloro-3-[2,2-difluoro-2-(1-oxidopyridin-2-yl)ethyl-amino]-2-oxo-1,2-dihydropyrazin-1-yl]-N-(3-fluoropyridin-2-ylmethyl)acetamide



C19 H16 Cl F3 N6 O3; Mol wt: 468.8214

ACTION – Antithrombotic agent with thrombin-inhibitory activity, a representative compound from a series of pyrazinone derivatives. Other specifically claimed compounds include the following:



Compound	R1	A	Formula
305930	F	CH	C ₂₀ H ₁₇ ClF ₃ N ₅ O ₃
305932	H	CH	C ₂₀ H ₁₈ ClF ₂ N ₅ O ₃
305933	Cl	N	C ₁₉ H ₁₆ Cl ₂ F ₂ N ₆ O ₃

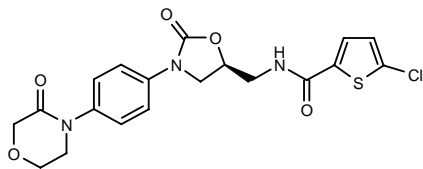
SOURCE – Merck & Co.

REFERENCES

1. Burgey, C. et al. (Merck & Co., Inc.) *Pyrazinone thrombin inhibitors*. WO 0138323.

307796

5-Chloro-*N*-[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-oxazolidin-5(*S*)-ylmethyl]thiophene-2-carboxamide



C19 H18 Cl N3 O5 S; Mol wt: 435.8862

ACTION – Anticoagulant and antithrombotic agent, a selective factor Xa inhibitor. *In vivo*, compound displayed potent antithrombotic activity in the rat arteriovenous shunt model, giving an ED₅₀ value of 3 mg/kg p.o. A specifically claimed compound from a series of substituted oxazolidinone derivatives.

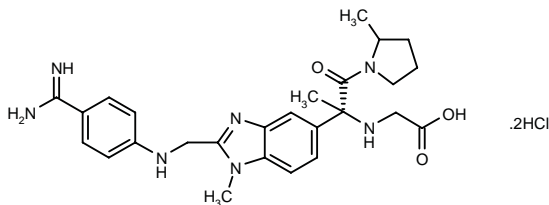
SOURCE – Bayer.

REFERENCES

1. Straub, A. et al. (Bayer AG) *Substd. oxazolidinones and their use in the field of blood coagulation*. DE 19962924, WO 0147919.

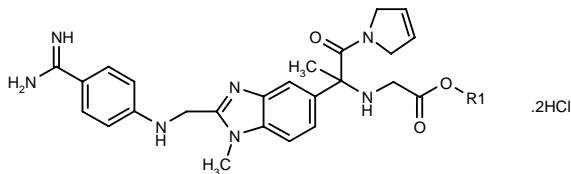
307798

2-[1(*R*)-[2-(4-Amidinophenylaminomethyl)-1-methyl-1*H*-benzimidazol-5-yl]-1-methyl-2-(2-methylpyrrolidin-1-yl)-2-oxoethylamino]acetic acid dihydrochloride



C26 H33 N7 O3 . 2HCl; Mol wt: 564.5145

ACTION – Antithrombotic agent, an inhibitor of thrombin and/or factor Xa shown to prolong the activated partial thromboplastin time (aPTT) with an ED₂₀₀ value (concentration doubling aPTT) of 0.12 μM. Other compounds from this series of benzimidazole derivatives include the following:



Compound	R1	Formula
307799	Et	C ₂₇ H ₃₃ N ₇ O ₃ .2HCl
307801	H	C ₂₅ H ₂₉ N ₇ O ₃ .2HCl

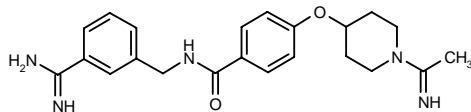
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Ries, U. et al. (Boehringer Ingelheim Pharma KG) *Benzimidazoles, production thereof and the use thereof*. DE 19962329, WO 0147896.

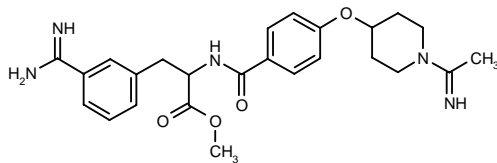
308263

N-(3-Amidinobenzyl)-4-[1-(ethanimidoyl)piperidin-4-yloxy]benzamide



C22 H27 N5 O2; Mol wt: 393.4883

ACTION – Antithrombotic agent, a factor Xa inhibitor (IC₅₀ = 0.059 μM) claimed to be useful for the treatment of acute coronary syndrome, myocardial infarction, unstable and refractory angina, occlusive coronary thrombus, stroke and venous thrombosis, among other disorders. Another specifically claimed bivalent phenylene compound is:



308265: C25 H31 N5 O4

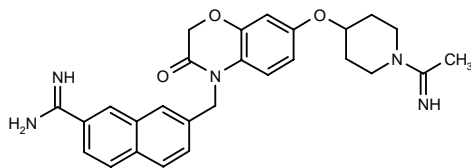
SOURCE – COR Therapeutics.

REFERENCES

1. Zhu, B.-Y. and Scarborough, R. (COR Therapeutics, Inc.) *Bivalent phenylene inhibitors of factor Xa*. WO 0156989.

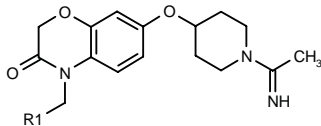
308267

7-[7-[1-(Ethanimidoyl)piperidin-4-yloxy]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-4-ylmethyl]naphthalene-2-carboxamidine



C27 H29 N5 O3; Mol wt: 471.5581

ACTION – Antithrombotic agent, a factor Xa inhibitor (IC₅₀ = 5.8 nM) claimed to be useful for the treatment of acute coronary syndrome, myocardial infarction, unstable and refractory angina, occlusive coronary thrombus, stroke and venous thrombosis, among other disorders. Other exemplified 3,4-dihydro-2*H*-benzo[1,4]oxazine derivatives are:



Compound	R1	Formula
308268	3-[3-[NH2C(=NH)]-Ph]-Ph	C ₂₉ H ₃₁ N ₅ O ₃
308270	3-[3-[NH2C(=NH)]-Ph]-5-isoxazolyl	C ₂₆ H ₂₈ N ₆ O ₄
308271	6-[NH2C(=NH)]-1-Me-2-indolyl	C ₂₆ H ₃₀ N ₆ O ₃
308273	6-[NH2C(=NH)]-1-Et-2-indolyl	C ₂₇ H ₃₂ N ₆ O ₃

SOURCE – COR Therapeutics.

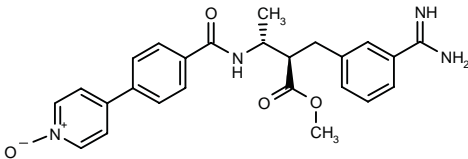
REFERENCES

1. Zhu, B.-Y. and Scarborough, R. (COR Therapeutics, Inc.) 3,4-Dihydro-2H-benzo[1,4]oxazine inhibitors of factor Xa. WO 0157003.

FXV-673

295864

2(R)-(3-Amidinobenzyl)-3(R)-[4-(1-oxidopyridin-4-yl)-benzamido]butyric acid methyl ester



C25 H26 N4 O4; Mol wt: 446.5044

ACTION – Anticoagulant, a factor Xa inhibitor (IC₅₀ = 0.52, 1.41 and 0.27 against human, dog and rabbit enzyme, respectively) with excellent selectivity (> 1,000-fold) relative to other serine proteases including thrombin, activated protein C, plasmin and tissue plasminogen activator (tPA). Compound prolonged plasma activated partial thromboplastin time (aPTT) and prothrombin time (PT) in a concentration-dependent manner, concentrations of 0.41, 0.65, 1.12 and 0.25 μM doubling aPTT in human, monkey, dog and rabbit plasma, respectively, and concentrations of 1.1, 1.32, 2.31 and 0.92 μM doubling the PT in human monkey, dog and rabbit plasma, respectively. Compound at concentrations of 1-100 μM did not inhibit platelet aggregation induced by ADP, collagen or TRAP1-6. In a canine model of electrolytic injury-induced carotid artery thrombosis in dogs, doses of 2.5-30 μg/kg/min i.v. significantly increased arterial blood flow and reduced the thrombus mass compared with placebo and heparin; similar results were found when compound was used as an adjunct during recombinant tPA-induced coronary artery thrombolysis in dogs. Interspecies extra-polation suggested that 100 ng/ml of compound would be an effective plasma concentration for clinical studies. Compound is undergoing clinical studies as an anti-thrombotic agent.

SOURCE – Aventis Pharma.

REFERENCES

1. Guertin, K.R. et al. (Aventis Pharma SA) Substd. N-[(aminoiminomethyl or aminomethyl)phenyl]propyl amides. EP 0906094, JP 2000502710, US 6080767, WO 9724118.

2. Klein, S.I. et al. (Aventis Pharmaceuticals, Inc.) Substd. N-[(aminoiminomethyl or aminomethyl)phenyl]propyl amides. CA 2264556, EP 0931060, JP 2001500532, WO 9900356.

3. Chu, V. et al. *Pharmacological characterization of a novel factor Xa inhibitor, FXV673*. Thromb Res 2001, 103(4): 309.

4. Rebello, S.S. et al. *Antithrombotic efficacy of a directed FXa inhibitor, FXV673, in a canine model of RT-PA-induced coronary artery thrombolysis*. Circulation 2000, 102(18, Suppl.): Abst 621.

5. Rebello, S.S. et al. *Antithrombotic efficacy of a novel factor Xa inhibitor, FXV673, in a canine model of coronary artery thrombolysis*. Br J Pharmacol 2001, 133(7): 1190.

6. Rebello, S.S. et al. *Role of short-term inhibition of factor Xa by FXV673 in arterial passivation: A study in a chronic model of thrombosis in conscious dogs*. Circulation 2000, 102(18, Suppl.): Abst 624.

7. Rebello, S.S. et al. *Role of short-term inhibition of factor Xa by FXV673 in arterial passivation: A study in a chronic model of thrombosis in conscious dogs*. J Cardiovasc Pharmacol 2001, 38(2): 288.

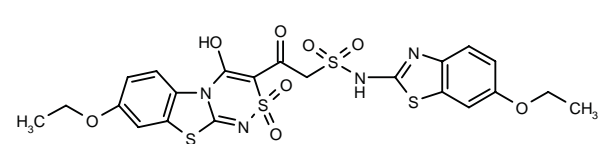
ANTIPLATELET THERAPY

CT-50547*

279097

N-(6-Ethoxybenzothiazol-2-yl)-2-(8-ethoxy-4-hydroxy-2,2-dioxo[1,2,4]thiadiazino[3,4-b]benzothiazol-3-yl)-2-oxoethane-1-sulfonamide

C-1330-7



C22 H20 N4 O8 S4; Mol wt: 596.6840

ACTION – Non-nucleoside platelet ADP receptor (P2Y₁₂, P2T_{AC}, P2Y_{ADP}, P2Y_{AC}, P2Y_{cyc}) antagonist (IC₅₀ = 0.17 μM for inhibition of [³H]-2-MeS-ADP binding to human P2Y₁₂ receptors) proven to inhibit ADP-induced aggregation of washed human platelets (IC₅₀ = 0.18 μM). Compound was also able to block ADP-induced K⁺ currents in *Xenopus* oocytes expressing the human P2Y₁₂ receptor (IC₅₀ = 40 nM) and showed 1,000-fold selectivity over cloned human P2Y₁ receptors in binding and functional assays (IC₅₀ > 100 μM). Potentially useful as an antithrombotic agent.

SOURCE – COR Therapeutics.

REFERENCES

1. Laibelman, A.M. et al. (COR Therapeutics, Inc.) Platelet ADP receptor inhibitors. EP 1047699, WO 9936425.

2. Conley, P.B. et al. *Molecular identification of the platelet ADP receptor targeted by antithrombotic drugs*. Blood 2000, 96(11, Part 1): Abst 949.

3. Hollopeter, G. et al. *Identification of the platelet ADP receptor targeted by antithrombotic drugs*. Nature 2001, 409(6817): 202.

4. Scarborough, R.M. et al. *Novel tricyclic benzothiazolo[2,3-c]thiadiazine antagonists of the platelet ADP receptor (P2Y12)*. Bioorg Med Chem Lett 2001, 11(14): 1805.

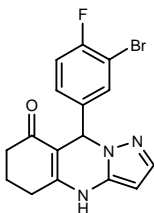
*Identified compound 279097 Drug Data Rep 1999, 021(10): 0890.

RENAL–UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

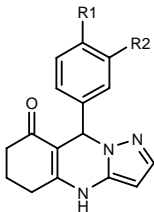
305494

(–)-9-(3-Bromo-4-fluorophenyl)-4,5,6,7,8,9-hexahydro-pyrazolo[5,1-*b*]quinazolin-8-one



C16 H13 Br F N3 O; Mol wt: 362.2007

ACTION – Potassium channel opener proven to induce 103% maximal steady-state membrane hyperpolarization relative to the reference compound P-1075 (assigned 100%) and to have an EC₅₀ value of 0.051 μM in guinea pig urinary bladder cells. The compound was also active in reducing stimulated contractions *in vitro* using isolated pig bladder strips, with 100% efficacy relative to P-1075 and a pD₂ value of 6.67. Claimed for the treatment of asthma, epilepsy, Raynaud’s syndrome, intermittent claudication, migraine, pain, pollakiuria, bladder instability, nocturia, bladder hyperreflexia, enuresis, alopecia, cardioprotection, ischemia, eating disorders, functional bowel disorders, neurodegeneration, bladder overactivity, benign prostatic hyperplasia, dysmenorrhea, preterm labor, urinary incontinence, male erectile dysfunction, premature ejaculation and female sexual dysfunction. Other exemplified compounds from this series of tricyclic dihydropyrimidine derivatives include the following:



Compound	R1	R2	Isomer	Formula
305495	F	Br	(+)	C ₁₆ H ₁₃ BrFN ₃ O
305496	Br	F		C ₁₆ H ₁₃ BrFN ₃ O

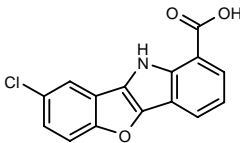
SOURCE – Abbott.

REFERENCES

1. Holladay, M.W. et al. (Abbott Laboratories Inc.) *Tricyclic dihydropyrimidine potassium channel openers*. US 6274587, WO 0136422.

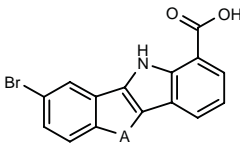
306946

8-Chloro-10*H*-[1]benzofuro[3,2-*b*]indole-1-carboxylic acid



C15 H8 Cl N O3; Mol wt: 285.6852

ACTION – Bladder-selective muscle relaxant (IC₅₀ = 5.8 and 268 μM for inhibition of precontracted rat detrusor strips and thoracic aorta strips, respectively) that probably acts via a mechanism involving activation of the large-conductance Ca²⁺-activated K⁺ (BK_{Ca}) channels. Potentially useful for the treatment of urinary incontinence. Other related compounds are:



Compound	A	Formula
306947	CH2	C ₁₆ H ₁₀ BrNO ₂
306948	O	C ₁₅ H ₈ BrNO ₃

SOURCE – American Home Products.

REFERENCES

1. Antane, S.A. et al. (American Home Products Corp.) *Substd. benzofuranoindoles and indenoindoles as novel potassium channel openers*. EP 1135393, US 6288099, WO 0034285.

2. Butera, J.A. et al. *Synthesis and potassium channel opening activity of substituted 10*H*-benzo[4,5]furo[3,2-*b*]indole- and 5,10-dihydro-indeno[1,2-*b*]indole-1-carboxylic acids*. Bioorg Med Chem Lett 2001, 11(16): 2093.

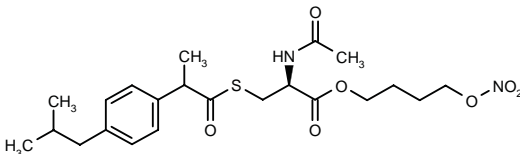
NCX-2111

308313

2(*S*)-Acetamido-3-[2-(4-isobutylphenyl)propionylsulfonyl]propionic acid 4-(nitrooxy)butyl ester

N-Acetyl-*S*-[2-(4-isobutylphenyl)propionyl]-D-cysteine 4-(nitrooxy)butyl ester

NO-ibuprofen



C22 H32 N2 O7 S; Mol wt: 468.5678

ACTION – Potent cyclooxygenase COX-1/COX-2 inhibitor, a nitric oxide (NO)-ibuprofen derivative that combines prostaglandin synthesis inhibition with NO-releasing activity. The compound exhibited good activity in both *in vitro* and *in vivo* in models of bladder hyper-reactivity. Potentially useful for the treatment of micturition disorders.

SOURCE – NicOx.

REFERENCES

1. Del Soldato, P. (NicOx SA) *Pharmaceutical cpds.* WO 0061537.

2. Riffaud, J.P. et al. *Antiproliferative potential of new NO-NSAIDs on human bladder and prostate cell lines.* Inflamm Res 2001, 50(Suppl. 3): Abst 071.

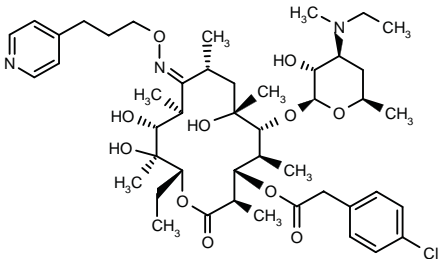
3. Riffaud, J.P. et al. *Pharmacological data obtained with a new NO-ibuprofen derivative (NCX 2111) on urinary bladder activity.* Inflamm Res 2001, 50(Suppl. 3): Abst 069.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

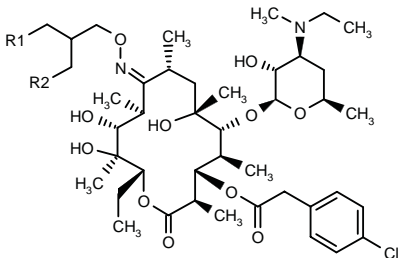
308254

3-*O*-[2-(4-Chlorophenyl)acetyl]-3'-*N*-demethyl-3-des(hexopyranosyl)-3'-*N*-ethylerythromycin A 9-[*O*-[3-(4-pyridyl)propyl]oxime]



C46 H70 Cl N3 O11; Mol wt: 876.5220

ACTION – Erythromycin derivative with antibacterial and antiulcer activity; it exerted potent activity *in vitro* against *Helicobacter pylori* strains TK1147, TK1308-CAM-r1, TK1308-CAM-r1 25-2 and TK1308-CAM-r1 25-3. Other exemplified macrolides are:



Compound	R1	R2	Formula
308256	H	H	C ₄₂ H ₆₉ ClN ₂ O ₁₁
308257	-(CH2)3-		C ₄₅ H ₇₃ ClN ₂ O ₁₁

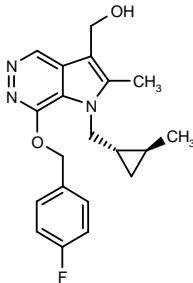
SOURCE – Hokuriku.

REFERENCES

1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *Erythromycin derivs.* JP 2001181294.

308605

1-[7-(4-Fluorobenzyloxy)-2-methyl-1-[(1*S*,2*S*)-2-methyl-cyclopropylmethyl]-1*H*-pyrrolo[2,3-*d*]pyridazin-3-yl]-methanol



C20 H22 F N3 O2; Mol wt: 355.4108

ACTION – Antiulcer agent, an inhibitor of H⁺/K⁺-ATPase (IC₅₀ = 0.015 µg/ml against enzyme from porcine gastric mucosa) with antimicrobial activity against *Helicobacter pylori* (MIC = 12.5 µg/ml or less against *H. pylori* strains 9470, 9472 and 9474). *In vivo*, compound was shown to inhibit gastric acid secretion stimulated by pylorus ligation in rats (ID₅₀ = 10 mg/kg p.o. or less). A representative compound from a series of pyrrolopyridazine derivatives.

SOURCE – Sankyo.

REFERENCES

1. Iwabuchi, H. et al. (Ube Industries, Ltd.) *Pyrrolopyridazine cpd.* WO 0158901.

D-002

305330

Mixture of aliphatic alcohols isolated and purified from beeswax (*Apis mellifera*), composed of triacontanol (25-35%), hexacosanol (7-20%), octacosanol (12-20%), tetracosanol (8-15%), dotriacontanol (18-25%) and tetratriacontanol (7.5% or less)

Beeswax alcohols
BWA
Abexol™

ACTION – Antiulcer agent, a natural extract from beeswax (*Apis mellifera*) with antioxidant and cytoprotective activity. Compound inhibited lipid peroxidation and increased superoxide dismutase activity in rat liver and brain microsomes. *In vivo*, it prevented indomethacin- and ethanol-induced ulcers, inhibited pylorus ligation-induced gastric ulcers without altering gastric secretion or pH, and protected guinea pigs against carrageenan-induced colonic ulceration. Randomized, double-blind, placebo-controlled studies in patients with gastric and duodenal ulcers showed significant improvement in ulcer healing rate and symptom relief compared with placebo. Compound is available in Cuba for the treatment of gastric ulcer and inflammatory bowel disease.

ACTION – Potent cyclooxygenase COX-1/COX-2 inhibitor, a nitric oxide (NO)-ibuprofen derivative that combines prostaglandin synthesis inhibition with NO-releasing activity. The compound exhibited good activity in both *in vitro* and *in vivo* in models of bladder hyper-reactivity. Potentially useful for the treatment of micturition disorders.

SOURCE – NicOx.

REFERENCES

1. Del Soldato, P. (NicOx SA) *Pharmaceutical cpds.* WO 0061537.

2. Riffaud, J.P. et al. *Antiproliferative potential of new NO-NSAIDs on human bladder and prostate cell lines.* Inflamm Res 2001, 50(Suppl. 3): Abst 071.

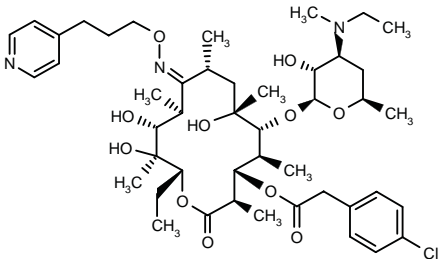
3. Riffaud, J.P. et al. *Pharmacological data obtained with a new NO-ibuprofen derivative (NCX 2111) on urinary bladder activity.* Inflamm Res 2001, 50(Suppl. 3): Abst 069.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

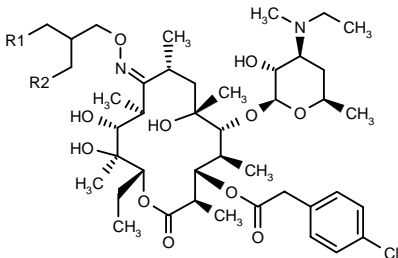
308254

3-*O*-[2-(4-Chlorophenyl)acetyl]-3'-*N*-demethyl-3-des(hexopyranosyl)-3'-*N*-ethylerythromycin A 9-[*O*-[3-(4-pyridyl)propyl]oxime]



C46 H70 Cl N3 O11; Mol wt: 876.5220

ACTION – Erythromycin derivative with antibacterial and antiulcer activity; it exerted potent activity *in vitro* against *Helicobacter pylori* strains TK1147, TK1308-CAM-r1, TK1308-CAM-r1 25-2 and TK1308-CAM-r1 25-3. Other exemplified macrolides are:



Compound	R1	R2	Formula
308256	H	H	C ₄₂ H ₆₉ ClN ₂ O ₁₁
308257	-(CH2)3-		C ₄₅ H ₇₃ ClN ₂ O ₁₁

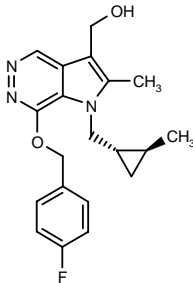
SOURCE – Hokuriku.

REFERENCES

1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *Erythromycin derivs.* JP 2001181294.

308605

1-[7-(4-Fluorobenzyloxy)-2-methyl-1-[(1*S*,2*S*)-2-methyl-cyclopropylmethyl]-1*H*-pyrrolo[2,3-*d*]pyridazin-3-yl]-methanol



C20 H22 F N3 O2; Mol wt: 355.4108

ACTION – Antiulcer agent, an inhibitor of H⁺/K⁺-ATPase (IC₅₀ = 0.015 µg/ml against enzyme from porcine gastric mucosa) with antimicrobial activity against *Helicobacter pylori* (MIC = 12.5 µg/ml or less against *H. pylori* strains 9470, 9472 and 9474). *In vivo*, compound was shown to inhibit gastric acid secretion stimulated by pylorus ligation in rats (ID₅₀ = 10 mg/kg p.o. or less). A representative compound from a series of pyrrolopyridazine derivatives.

SOURCE – Sankyo.

REFERENCES

1. Iwabuchi, H. et al. (Ube Industries, Ltd.) *Pyrrolopyridazine cpd.* WO 0158901.

D-002

305330

Mixture of aliphatic alcohols isolated and purified from beeswax (*Apis mellifera*), composed of triacontanol (25-35%), hexacosanol (7-20%), octacosanol (12-20%), tetracosanol (8-15%), dotriacontanol (18-25%) and tetratriacontanol (7.5% or less)

Beeswax alcohols
BWA
Abexol™

ACTION – Antiulcer agent, a natural extract from beeswax (*Apis mellifera*) with antioxidant and cytoprotective activity. Compound inhibited lipid peroxidation and increased superoxide dismutase activity in rat liver and brain microsomes. *In vivo*, it prevented indomethacin- and ethanol-induced ulcers, inhibited pylorus ligation-induced gastric ulcers without altering gastric secretion or pH, and protected guinea pigs against carrageenan-induced colonic ulceration. Randomized, double-blind, placebo-controlled studies in patients with gastric and duodenal ulcers showed significant improvement in ulcer healing rate and symptom relief compared with placebo. Compound is available in Cuba for the treatment of gastric ulcer and inflammatory bowel disease.

SOURCES – Centro Nacional de Investigaciones Científicas, La Habana (CU); Laboratorios Dalmer.

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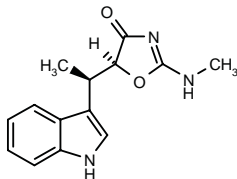
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TAK-083

308277

5(S)-[1(R)-(1*H*-Indol-3-yl)ethyl]-2-(methylamino)oxazol-4(5*H*)-one

Indolmycin
PA-155A



C14 H15 N3 O2; Mol wt: 257.2915

ACTION – Antibacterial agent isolated from the fermentation broth of *Streptomyces* sp. strain HC-21, with potent and selective activity against *Helicobacter pylori*, proven to be more potent than amoxicillin, clarithromycin or metronidazole against 54 clinical isolates of *H. pylori* (MIC₉₀ = 0.031, 0.125, 64 and 8 µg/ml, respectively). Bactericidal activity was seen against all strains tested following exposure at the MIC or greater concentrations. Compound acts by inhibiting tryptophanyl-tRNA synthetase (tryptophan–tRNA ligase) and was inactive against common aerobic and anaerobic bacteria. No significant changes in susceptibilities to TAK-083 were seen upon repeated exposure to subinhibitory concentrations of the drug. *In vivo*, it protected Mongolian gerbils from infection by *H. pylori* and complete elimination of bacteria in the gastric wall was seen with the dose of 10 mg/kg p.o. b.i.d. for 7 days.

SOURCE – Takeda.

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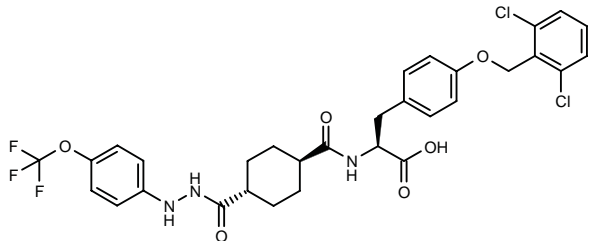
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AGENTS FOR INFLAMMATORY
BOWEL DISEASE

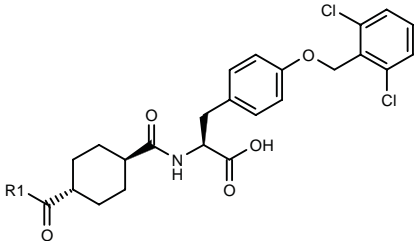
307394

O-(2,6-Dichlorobenzyl)-*N*-[*trans*-4-[2-[4-(trifluoromethoxy)phenyl]hydrazinocarbonyl]cyclohexylcarbonyl]-L-tyrosine



C31 H30 Cl2 F3 N3 O6; Mol wt: 668.4930

ACTION – $\alpha_4\beta_7$ integrin inhibitor with selectivity over $\alpha_4\beta_1$ integrin, potentially useful in the treatment or prevention of inflammatory bowel disease, diabetes and tumor growth and metastasis. In binding assays, compound exhibited an IC_{50} value of 0.2 μM or less for inhibition of human VCAM-1 binding to RPMI-8866 cells expressing $\alpha_4\beta_7$ integrin, compared to an IC_{50} value in the range of 25-50 μM for inhibition of human VCAM-1 binding to human Jurkat cells expressing $\alpha_4\beta_1$ integrin; in addition, it inhibited the binding of rat MadCAM to RPMI-8866 cells expressing $\alpha_4\beta_7$ integrin with an IC_{50} value in the range of 1-5 μM . Other exemplified compounds from this series of phenylalanine derivatives include the following:



Compound	R1	Formula
307395	OH	C ₂₄ H ₂₅ Cl ₂ N ₃ O ₆
307396	NHNHPh	C ₃₀ H ₃₁ Cl ₂ N ₃ O ₅
307398	4-MeO-PhNHNH	C ₃₁ H ₃₃ Cl ₂ N ₃ O ₆
307399	4-CN-PhNHNH	C ₃₁ H ₃₀ Cl ₂ N ₄ O ₅
307400	4-Me-PhNHNH	C ₃₁ H ₃₃ Cl ₂ N ₃ O ₅
307402	3-MeO-PhNHNH	C ₃₁ H ₃₃ Cl ₂ N ₃ O ₆

SOURCE – Ajinomoto.

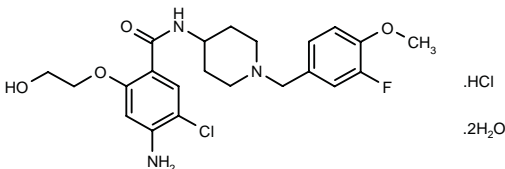
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1. Tanaka, Y. et al. (Ajinomoto Co., Inc.) *Novel phenylalanine derivs.* WO 0147868.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

305448

4-Amino-5-chloro-*N*-[1-(3-fluoro-4-methoxybenzyl)-piperidin-4-yl]-2-(2-hydroxyethoxy)benzamide hydrochloride dihydrate



C₂₂ H₂₇ Cl F N₃ O₄ . HCl . 2H₂O; Mol wt: 524.4138

ACTION – A representative compound from a series of hydroxyethoxybenzamide derivatives with combined dopamine D2 receptor-antagonist and 5-HT₄ receptor-agonist activity, potentially useful for improving digestive tract function, in particular for the treatment of reflux esophagitis, unidentified epigastric complaints, gastritis and gastric ulcer. *In vitro*, it gave a K_i value of 7.0 nM against [³H]-spiperone binding to D2 receptors in rat striatal membrane homogenates and was shown to relax carbachol-induced contractions of rat esophageal sphincter muscularis mucosae with an EC_{50} value of

61 nM. *In vivo*, it was shown to dose-dependently (3-30 mg/kg p.o.) promote gastric motility in rats, being more potent than domperidone, mosapride and cisapride, and it was effective against apomorphine-induced emesis (ED_{80} = 0.39 mg/kg p.o. vs. 0.23 mg/kg p.o. for domperidone). In acute toxicity studies in rats, compound gave an LD_{50} value > 2000 mg/kg p.o.

SOURCE – Kissei.

REFERENCES

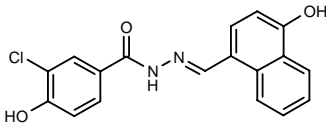
1. Okazaki, K. et al. (Kissei Pharmaceutical Co., Ltd.) *Hydroxyethoxybenzamide derivs. and drugs containing the same.* WO 0136385.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

292750

3-Chloro-4-hydroxy-*N*²-(4-hydroxynaphthalen-1-ylmethylidene)benzohydrazide



C₁₈ H₁₃ Cl N₂ O₃; Mol wt: 340.7647

ACTION – Glucagon receptor antagonist with sub-micromolar affinity for human and rat glucagon receptors (IC_{50} = 0.20 and 0.0042 μM , respectively) and competitive antagonist activity at human glucagon receptors (pA_2 = 6.99 against glucagon-induced cAMP accumulation in BHK cells transfected with the human receptor). *In vivo*, compound dose-dependently (0.1-1.0 mg/kg i.v.) inhibited the glucagon-induced hyperglycemic response in rats, but it did not affect plasma glucose levels when given alone. Potentially useful for the treatment of type 2 diabetes.

SOURCES – Novo Nordisk; Pfizer.

REFERENCES

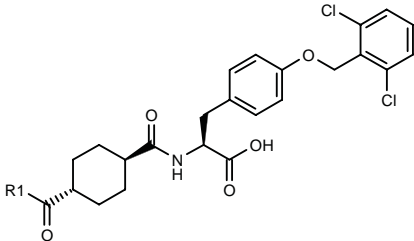
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2. Ling, A. et al. (Novo Nordisk A/S; Agouron Pharmaceuticals, Inc.) *Glucagon antagonists/inverse agonists.* WO 0039088.

3. Ling, A. et al. *Identification of alkylidene hydrazides as glucagon receptor antagonists.* J Med Chem 2001, 44(19): 3141.

4. Madsen, P. et al. *Alkylidene hydrazides as potent human glucagon receptor antagonists: Further structure-activity relationships and in vivo studies.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 167.

ACTION – $\alpha_4\beta_7$ integrin inhibitor with selectivity over $\alpha_4\beta_1$ integrin, potentially useful in the treatment or prevention of inflammatory bowel disease, diabetes and tumor growth and metastasis. In binding assays, compound exhibited an IC_{50} value of 0.2 μM or less for inhibition of human VCAM-1 binding to RPMI-8866 cells expressing $\alpha_4\beta_7$ integrin, compared to an IC_{50} value in the range of 25-50 μM for inhibition of human VCAM-1 binding to human Jurkat cells expressing $\alpha_4\beta_1$ integrin; in addition, it inhibited the binding of rat MadCAM to RPMI-8866 cells expressing $\alpha_4\beta_7$ integrin with an IC_{50} value in the range of 1-5 μM . Other exemplified compounds from this series of phenylalanine derivatives include the following:



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SOURCE – Ajinomoto.

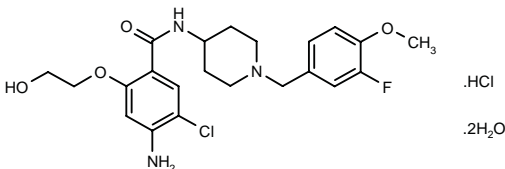
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TREATMENT OF DISORDERS OF GASTRIC EMPTYING

305448

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SOURCE – Kissei.

REFERENCES

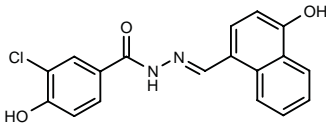
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

292750

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SOURCES – Novo Nordisk; Pfizer.

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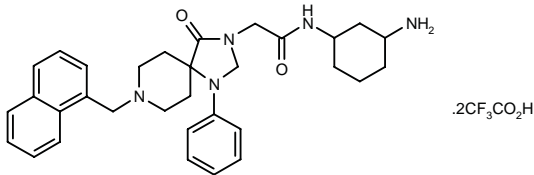
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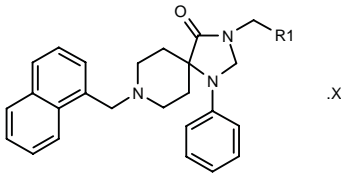
305462

N-(3-Aminocyclohexyl)-2-[8-(naphthalen-1-ylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetamide bis(trifluoroacetate)



C32 H39 N5 O2 . 2 C2 H F3 O2; Mol wt: 753.7369

ACTION – Agent with high affinity for nociceptin (N/OFQ, ORL1, NOP) receptors, potentially useful for the treatment of type 2 diabetes, septic shock, inflammation, incontinence and vasomotor disturbances, particularly the peripheral vasomotor effects known as hot flushes or hot flashes. Other exemplified compounds from this series of triazaspirodecanones are:



Compound	R1	X	Formula
305463	trans-2-NH2-cyclohexyl-NHCO	2CF3CO2H	C ₃₂ H ₃₉ N ₅ O ₂ .2C ₂ HF ₃ O ₂
305465	trans-4-NH2-cyclohexyl-NHCO	2CF3CO2H	C ₃₂ H ₃₉ N ₅ O ₂ .2C ₂ HF ₃ O ₂
305466	CH2NHCH2CH2-N(CH2CH2NH2)2	.4CF3CO2H	C ₃₂ H ₄₅ N ₇ O ₂ .4C ₂ HF ₃ O ₂
305468	CH2CH2NHCH2-CH2N(CH2CH2NH2)2	.4CF3CO2H	C ₃₃ H ₄₇ N ₇ O ₂ .4C ₂ HF ₃ O ₂
305469	CH2NH(CH2)3-N[(CH2)3NH2]2	.4CF3CO2H	C ₃₅ H ₅₁ N ₇ O ₂ .4C ₂ HF ₃ O ₂
305472	CH2CH2NH(CH2)3-N[(CH2)3NH2]2	.4CF3CO2H	C ₃₆ H ₅₃ N ₇ O ₂ .4C ₂ HF ₃ O ₂
305475	(CH2)3NH(CH2)3-N[(CH2)3NH2]2	.4CF3CO2H	C ₃₇ H ₅₅ N ₇ O ₂ .4C ₂ HF ₃ O ₂
305476	(CH2)3NHCH2-CH2N(CH2CH2NH2)2	4HCl	C ₃₄ H ₄₉ N ₇ O ₂ .4HCl
305477	CONHCH2CH2-N(CH2CH2NH2)2	4HCl	C ₃₂ H ₄₃ N ₇ O ₂ .4HCl
305478	CONH(CH2)3N[(CH2)3NH2]2	.3CF3CO2H	C ₃₅ H ₄₉ N ₇ O ₂ .3C ₂ HF ₃ O ₂

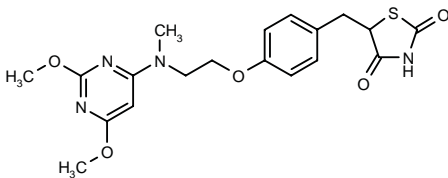
SOURCE – Novo Nordisk.

REFERENCES

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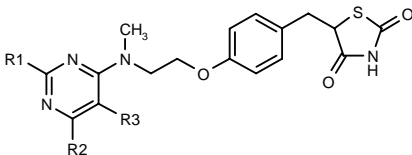
305516

5-[4-[2-[*N*-(2,6-Dimethoxypyrimidin-4-yl)-*N*-methylamino]-ethoxy]benzyl]thiazolidine-2,4-dione



C19 H22 N4 O5 S; Mol wt: 418.4718

ACTION – Agent for the treatment of hyperglycemia, hyperlipidemia and complications associated with insulin resistance such as hypertension, hyperuricemia and other cardiovascular, metabolic and endocrine disorders, either alone or in combination with another antidiabetic agent, proven to decrease blood glucose levels by 53% in diabetic *db/db* mice at 1 mg/kg/day p.o. x 5 days, being more potent than troglitazone (38% decrease at 100 mg/kg/day p.o. x 5 days). Other specifically claimed compounds from this series of thiazolidinedione derivatives are:



Compound	R1	R2	R3	Formula
305517	H	H	H	C ₁₇ H ₁₈ N ₄ O ₃ S
305519	H	Cl	H	C ₁₇ H ₁₇ ClN ₄ O ₃ S
305520	NH2	Cl	H	C ₁₇ H ₁₈ ClN ₅ O ₃ S
305522	H	-N=CHNH-		C ₁₈ H ₁₈ N ₆ O ₃ S
305523	H	-N(Me)CH=N-		C ₁₉ H ₂₀ N ₆ O ₃ S
305524	H	OMe	H	C ₁₈ H ₂₀ N ₄ O ₄ S
305525	H	OH	H	C ₁₇ H ₁₈ N ₄ O ₄ S

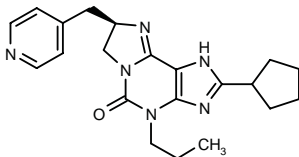
SOURCE – Vita-Invest.

REFERENCES

1. Mourelle Mancini, M. et al. (Vita-Invest, SA) *Novel thiazolidinedione derivs. as antidiabetic agents*. WO 0136416.

307407

2-Cyclopentyl-4-propyl-8(*R*)-(pyridin-4-ylmethyl)-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*f*]purin-5-one



C21 H26 N6 O; Mol wt: 378.4774

ACTION – A representative compound from a series of fused purine derivatives with antidiabetic properties. It produced an increase in insulin secretion in pancreatic β -cells after glucose loading. *In vivo*, it displayed glucose-lowering activity following p.o. administration to normal rats (14 mg/kg) and it showed a minimum lethal dose (MLD) of > 500 mg/kg p.o. in mice.

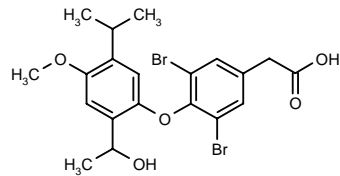
SOURCE – Kyowa Hakko.

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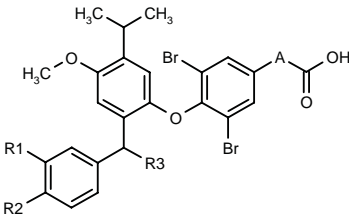
307901

2-[3,5-Dibromo-4-[2-(1-hydroxyethyl)-5-isopropyl-4-methoxyphenoxy]phenyl]acetic acid



C20 H22 Br2 O5; Mol wt: 502.1968

ACTION – Liver-selective glucocorticoid receptor antagonist with glucose-lowering activity, potentially useful for the treatment of diabetes, Cushing's syndrome and inflammation. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	A	Formula
307902	Me	H	OMe	-CH2-	C ₂₇ H ₂₈ Br ₂ O ₅
307903	Me	H	i-PrNH	-CH2-	C ₂₉ H ₃₃ Br ₂ NO ₄
307904	Me	H	4-OH-PhCONH	-CH2-	C ₃₃ H ₃₁ Br ₂ NO ₆
307905	I	H	OH	-CH2-	C ₂₅ H ₂₃ Br ₂ IO ₅
307906	Me	F	OH	-CH2-	C ₂₆ H ₂₆ Br ₂ FO ₅
307907	Me	H	OH	-(CH2)2-	C ₂₇ H ₂₈ Br ₂ O ₅

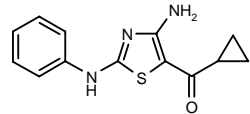
SOURCES – Abbott; Karo Bio.

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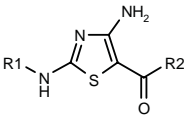
308324

1-[4-Amino-2-(phenylamino)thiazol-5-yl]-1-cyclopropyl-methanone



C13 H13 N3 O S; Mol wt: 259.3317

ACTION – Glycogen synthase kinase 3 (GSK-3) inhibitor (IC₅₀ < 5 μM) that is expected to be useful for the treatment of type 1 and type 2 diabetes, impaired glucose tolerance, obesity, Alzheimer's disease and bipolar disorder. Other exemplified 2,4-diaminothiazole derivatives are:



Compound	R1	R2	Formula
308325	Ph	Et	C ₁₂ H ₁₃ N ₃ OS
308326	Pr	3-Pyr	C ₁₂ H ₁₄ N ₄ OS
308327	Ph	3-thienyl	C ₁₄ H ₁₁ N ₃ OS ₂
308328	Ph	Me	C ₁₁ H ₁₁ N ₃ OS
308329	3,4-(Cl)2-Ph	3-(PhCH2O)-Ph	C ₂₃ H ₁₇ Cl ₂ N ₃ O ₂ S
308330	Et	Ph	C ₁₂ H ₁₃ N ₃ OS

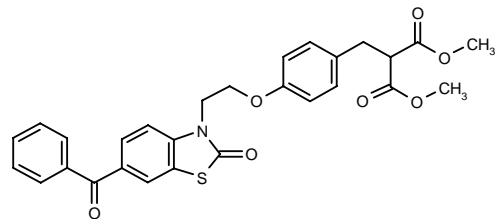
SOURCE – Novo Nordisk.

REFERENCES

1. Bowler, A.N. et al. (Novo Nordisk A/S) *2,4-Diaminothiazole derivs*. WO 0156567.

308378

2-[4-[2-(6-Benzoyl-2-oxo-2,3-dihydrobenzothiazol-3-yl)ethoxy]benzyl]malonic acid dimethyl diester



C28 H25 N O7 S; Mol wt: 519.5715

ACTION – Hypoglycemic agent proven to lower glucose levels by 43 and 45%, respectively, when given to diabetic *ob/ob* mice at 30 mg/kg/day b.i.d. p.o. x 4 days and 10 mg/kg/day b.i.d. i.p. x 4 days, reported to exhibit fewer side effects than other hypoglycemic agents such as thiazolidinedione derivatives.

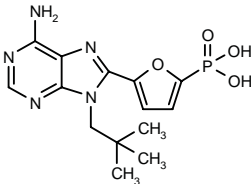
SOURCE – ADIR.

REFERENCES

1. Lesieur, D. et al. (ADIR et Cie.) *Condensed azole derivatives and their use as hypoglycemic agents*. FR 2804431, WO 0157002.

308602

5-[6-Amino-9-(2,2-dimethylpropyl)-9*H*-purin-8-yl]furan-2-ylphosphonic acid



C14 H18 N5 O4 P; Mol wt: 351.3012

ACTION – A representative compound from a series of purine-containing phosphonic acids that inhibit fructose-1,6-bisphosphatase (FBPase) at the AMP site. This compound gave an IC_{50} of 0.8 μ M against FBPase from human liver, and was at least 125-fold selective over other AMP-binding enzymes. In rat hepatocytes, it was shown to inhibit the production of glucose from lactate/pyruvate and dihydroxyacetone with IC_{50} values of 4.5 and 5 μ M, respectively. The glucose-lowering activity of this compound was demonstrated in a series of *in vivo* tests in rats, following either direct administration or in prodrug form. Potentially useful for the treatment of conditions associated with elevated glucose or insulin levels, particularly diabetes and atherosclerosis.

SOURCE – Metabasis Therapeutics.

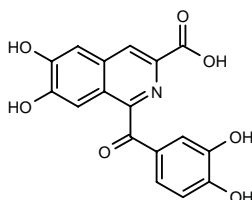
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1. Dang, Q. et al. (Metabasis Therapeutics, Inc.) *Purine inhibitors of fructose 1,6-bisphosphatase*. US 6284748.

NBI-31772

309021

1-(3,4-Dihydroxybenzoyl)-6,7-dihydroxyisoquinoline-3-carboxylic acid



C17 H11 N O7; Mol wt: 341.2739

ACTION – Nonpeptide ligand able to displace insulin growth factor-I (IGF-I) from all IGF-binding proteins (IGFBPs) at subnanomolar concentrations ($K_i = 1.18$ -16.60 nM). Compound reversed the neutralizing effect of human IGFBP-3 on the proliferative effects of hIGF-I in 3T3 fibroblasts, demonstrating its ability to release free bioactive IGF-I. Potentially useful for the treatment of diabetes and related disorders.

SOURCE – Neurocrine Biosciences.

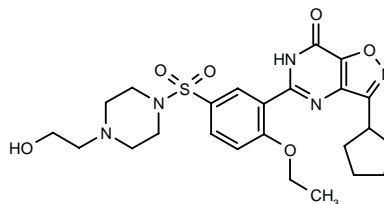
REFERENCES

1. Chen, C. et al. *Discovery of a series of nonpeptide small molecules that inhibit the binding of insulin-like growth factor (IGF) to IGF-binding proteins*. J Med Chem 2001, 44(23): 4001.
2. Liu, X.J. et al. *Identification of a nonpeptide ligand that releases bioactive insulin-like growth factor-I from its binding protein complex*. J Biol Chem 2001, 276(35): 32419.

TREATMENT OF MALE SEXUAL DYSFUNCTION

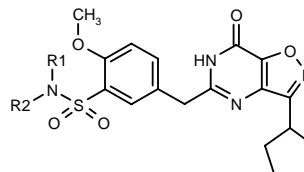
307803

3-Cyclopentyl-5-[2-ethoxy-5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]phenyl]isoxazolo[4,5-*d*]pyrimidin-7(6*H*)-one

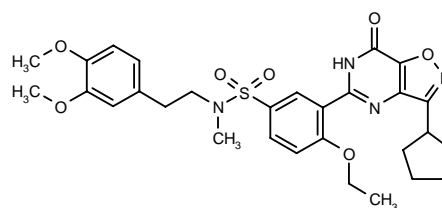


C24 H31 N5 O6 S; Mol wt: 517.6039

ACTION – An inhibitor of cGMP-phosphodiesterases, claimed for the treatment or prevention of cardiovascular and cerebrovascular disorders and disorders of the urogenital tract such as erectile dysfunction and female sexual dysfunction. Other exemplified compounds within this series isoxazolo[4,5-*d*]pyrimidin-7(6*H*)-one derivatives are:



Compound	R1	R2	Formula
307806	-CH2CH2N(Me)CH2CH2-		C ₂₃ H ₂₉ N ₅ O ₅ S
307807	-CH2CH2CH(OH)CH2CH2-		C ₂₃ H ₂₈ N ₄ O ₆ S
307808	4-Pyr	H	C ₂₃ H ₂₃ N ₅ O ₅ S
307809	3-F-4-MeO-Ph	H	C ₂₅ H ₂₅ FN ₄ O ₆ S



307804: C29 H34 N4 O7 S

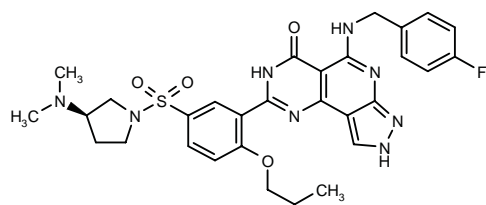
SOURCE – Bayer.

REFERENCES

1. Niewöhner, U. et al. (Bayer AG) *Isoxazolo pyrimidinones and the use thereof*. DE 19962925, WO 0147934.

308560

2-[5-[3(R)-(Dimethylamino)pyrrolidin-1-ylsulfonyl]-2-propoxyphenyl]-5-(4-fluorobenzylamino)-4,8-dihydro-3H-pyrazolo[4',3':5,6]pyrido[4,3-d]pyrimidin-4-one



C30 H33 F N8 O4 S; Mol wt: 620.7067

ACTION – Potent and selective inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 0.31 nM) with 160-fold selectivity over PDE6 and more than 10,000-fold selectivity over PDE1, PDE2, PDE3 and PDE4 isozymes. Compared to sildenafil, compound exhibited only a 6-fold improvement in potency but much higher selectivity. Potentially useful for the treatment of erectile dysfunction.

SOURCE – Bristol-Myers Squibb.

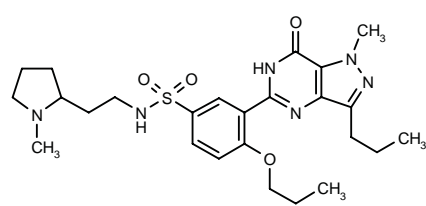
REFERENCES

1. Bi, Y. et al. *The discovery of novel, potent and selective PDE5 inhibitors.* Bioorg Med Chem Lett 2001, 11(18): 2461.

DA-8159*

290189

3-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide



C25 H36 N6 O4 S; Mol wt: 516.6634

ACTION – Selective phosphodiesterase type 5 (PDE5) inhibitor with superior isozyme selectivity, longer half-life and reduced hepatic metabolism compared to sildenafil. Compound induced concentration-dependent (1 nM-1 μM) relaxation of phenylephrine-contracted rabbit corpus cavernosum and potentiated the relaxant effects of sodium nitroprusside on phenylephrine-precontracted preparations. *In vivo*, it increased the number of erections in rats (0.3-1 mg/kg p.o.), with comparable effects to sildenafil, and potentiated the increase in intracavernosal pressure induced by intracavernosal sodium nitroprusside in anesthetized dogs (1-300 μg/kg i.v.). Furthermore, the drug exhibited a preclinical toxicity profile in mice and rats superior to that of sildenafil. Compound recently entered phase I trials for the treatment of erectile dysfunction.

SOURCE – Dong-A.

REFERENCES

1. Yoo, M. et al. (Dong-A Pharmaceutical Co., Ltd.) *Pyrazolopyrimidinone derivs. for the treatment of impotence.* EP 1129093, WO 0027848.

2. Ahn, B. et al. *DA-8159, a selective phosphodiesterase-5 inhibitor, increases intracavernosal pressure in anesthetized rats and dogs.* Int J Impot Res 2001, 13(Suppl. 1): Abst P43.

3. Ahn, B.O. et al. *Preclinical toxicity of a new phosphodiesterase-5 inhibitor DA-8159.* Aging Male 2001, 4(Suppl. 1): Abst 50.

4. Oh, T.Y. et al. *Erectogenic effect of the selective phosphodiesterase type 5 inhibitor, DA-8159.* Arch Pharmacol Res 2000, 23(5): 471.

5. Shim, H.J. et al. *Factors influencing the protein binding of a new phosphodiesterase V inhibitor, DA-8159, using an equilibrium dialysis technique.* Biopharm Drug Dispos 2000, 21(7): 285.

6. Yoo, M. et al. *In vivo efficacy and in vitro metabolism of DA-8159, a novel phosphodiesterase-5 inhibitor.* Aging Male 2001, 4(Suppl. 1): Abst 49.

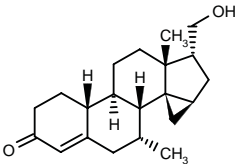
7. *DA-8159 in clinical testing for erectile dysfunction.* DailyDrugNews.com (Daily Essentials) 2001, Oct 1.

*Identified compound **290189** Drug Data Rep 2000, 022(09): 0810.

CONTRACEPTIVES

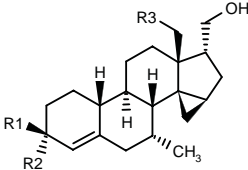
306312

17α-(Hydroxymethyl)-7α-methyl-14β,15β-methyleneestr-4-en-3-one



C21 H30 O2; Mol wt: 314.4660

ACTION – Steroid with androgenic activity, indicated for male contraception and male hormone replacement therapy, as well as for androgen replacement therapy in postmenopausal women or in androgen-deficient children. Other exemplified steroids with a 14β,15β-cyclopropane ring and a 17α-hydroxymethyl moiety are:



Compound	R1	R2	R3	Formula
306313		-O-	Me	C ₂₂ H ₃₂ O ₂
306314	OH	H	H	C ₂₁ H ₃₂ O ₂

SOURCE – Akzo Nobel.

REFERENCES

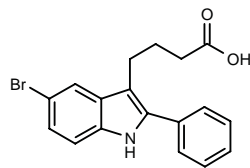
1. Leysen, D. et al. (Akzo Nobel N.V.) *Novel androgens.* WO 0140255.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

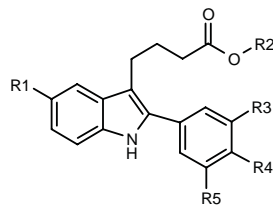
305669

4-(5-Bromo-2-phenyl-1*H*-indol-3-yl)butyric acid



C18 H16 Br N O2; Mol wt: 358.2334

ACTION – An inhibitor of the action of CXC chemokines such as IL-8, Gro, NAP-2 and ENA-78, with potential for the treatment of disorders mediated by chemokine receptors such as rheumatoid arthritis, acute respiratory distress syndrome, psoriasis, Crohn’s disease and any disorder associated with massive neutrophil infiltration. Other exemplified compounds from this series of substituted indole derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
305670	CF3	H	H	H	H	C ₁₉ H ₁₆ F ₃ NO ₂
305671	Cl	H	H	Cl	Cl	C ₁₈ H ₁₄ Cl ₃ NO ₂
305673	Cl	Na	H	F	H	C ₁₈ H ₁₄ ClFNNaO ₂
305674	Cl	H	H	Cl	F	C ₁₈ H ₁₄ Cl ₂ FNO ₂
305675	Cl	H	H	F	Me	C ₁₉ H ₁₇ ClFNO ₂
305676	Cl	H	Me	F	Me	C ₂₀ H ₁₉ ClFNO ₂
305677	Cl	H	H	Cl	CF3	C ₁₉ H ₁₄ Cl ₂ F ₃ NO ₂

SOURCE – Fournier.

REFERENCES

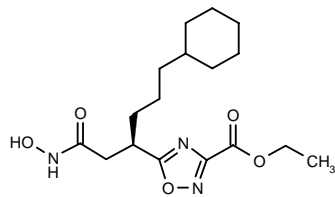
1. Paquet, J.-L. et al. (Fournier Industrie et Santé) *Novel IL-8 receptor antagonists*. FR 2801585, WO 0138305.

WOUND-HEALING AGENTS

307736

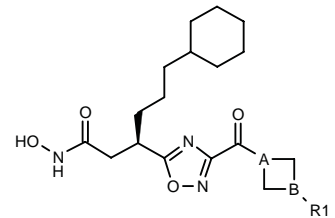
5-[4-Cyclohexyl-1-(*R*)-(N-hydroxycarbamoylmethyl)butyl]-1,2,4-oxadiazole-3-carboxylic acid ethyl ester

6-Cyclohexyl-3(*R*)-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanohydroxamic acid



C17 H27 N3 O5; Mol wt: 353.4163

ACTION – Procollagen C-proteinase (PCP) inhibitor that is selective over matrix metalloproteinases MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-9 (gelatinase B) and MMP-14, and has potential in the treatment of collagen-mediated conditions including the antiscarring treatment of wounds. Other exemplified oxazolyl- and oxadiazolyl-hydroxamic acids include the following:



Compound	R1	A	B	Formula
307737	t-BuOCO	CH	N	C ₂₃ H ₃₇ N ₅ O ₆
307738	H	CH	N	C ₁₈ H ₂₉ N ₅ O ₄
307739	NH2	N	CH	C ₁₈ H ₂₉ N ₅ O ₄

SOURCE – Pfizer.

REFERENCES

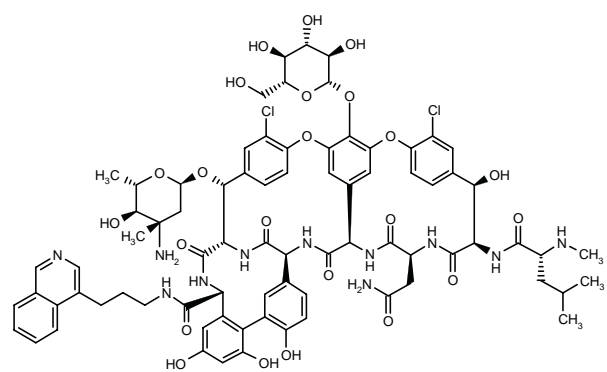
1. Bailey, S. et al. (Pfizer Ltd.;Pfizer Inc.) *Ox(adi)azolyl-hydroxamic acids useful as procollagen C-proteinase inhibitors*. WO 0147901.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

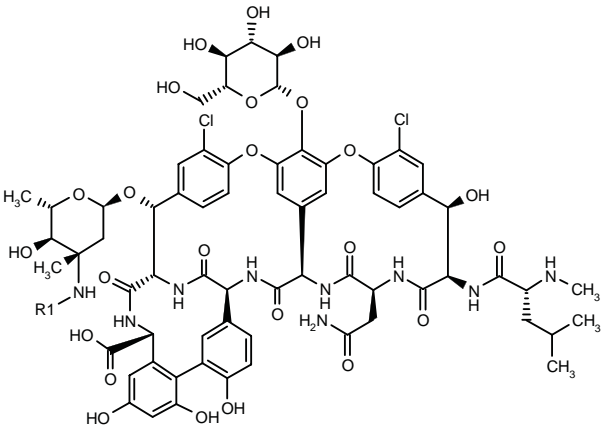
307242

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*S*,38*aR*)-22-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-L-arabinohexopyranosyloxy)-3-(carbamoylmethyl)-10,19-dichloro-44-(β-D-glucopyranosyloxy)-*N*-[3-(4-isoquinolyl)propyl]-7,28,30,32-tetrahydroxy-*N*-methyl-6-(*N*²-methyl-D-leucylamido)-2,5,24,38,39-pentaoxo-1,2,3,4,5,6,7,22,23,24,25,26,36,37,38,38*a*-hexadecahydro-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclopentacosine-26-carboxamide



C78 H87 Cl2 N11 O23; Mol wt: 1617.5050

ACTION – Antibacterial agent active against methicillin-resistant bacteria and vancomycin-resistant *Enterococcus*, as demonstrated *in vitro* by MIC values of 0.2, 6.25 and 3.13 µg/ml, respectively, against methicillin-resistant *Staphylococcus aureus* SR3637 and vancomycin-resistant *Enterococcus faecalis* SR7914 and *Enterococcus faecium* SR7917; MIC values for vancomycin were 1.56, > 100 and > 100 µg/ml, respectively. Other compounds from this series of glycopeptides include the following:



Compound	R1	Formula
307243	4-(4-Cl-PhCH=CH)-PhCH2	C ₈₁ H ₈₆ Cl ₃ N ₉ O ₂₄
307244	4-(4-Cl-Ph)-PhCH2	C ₇₉ H ₈₄ Cl ₃ N ₉ O ₂₄
307245	4-[4-EtO-PhC(Cl)=CH]-PhNHCO	C ₈₃ H ₈₉ Cl ₃ N ₁₀ O ₂₆

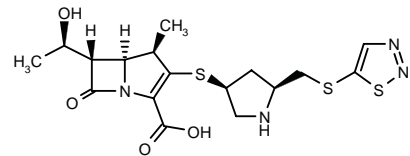
SOURCE – Shionogi.

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308005

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*S*)-(1,2,3-thiadiazol-5-ylsulfanylmethyl)pyrrolidin-3(*S*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid



C17 H22 N4 O4 S3; Mol wt: 442.5828

ACTION – Carbapenem antibiotic with broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* (MIC = 0.013-0.049 µg/ml), *Streptococcus pyogenes* (MIC = 0.007 µg/ml), *Pseudomonas aeruginosa* (MIC = 0.195-1.563 µg/ml) and *Escherichia coli* (MIC = 0.013 µg/ml). Compound exhibited good stability to dehydropeptidase (DHP-I) and an excellent pharmacokinetic profile in rats after i.v. administration, with a 10-fold longer half-life and 6-fold higher AUC values than meropenem.

SOURCE – Korea Institute of Science & Technology, Seoul (KR).

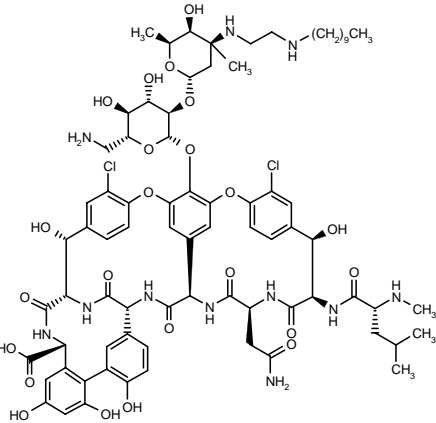
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308377

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-3-(Carbamoylmethyl)-10,19-dichloro-44-[6-amino-2-*O*-[3-[2-(decylamino)ethylamino]-3-*C*-methyl-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]-6-deoxy-β-D-glucopyranosyloxy]-7,22,28,30,32-pentahydroxy-6-(*N*-methyl-D-leucylamino)-2,5,24,38,39-pentaoxo-1,2,3,4,5,6,7,22,23,24,25,26,36,37,38,38*a*-hexa-decahydro-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino-[4,5-*m*]-[10,2,16]benzoxadiazacyclopentacosine-26-carboxylic acid

6'-Amino-3''-*N*-[2-(decylamino)ethyl]-6'-deoxyvancomycin



C78 H101 Cl2 N11 O23; Mol wt: 1631.6160

ACTION – Antibacterial agent reported to be particularly useful for the treatment of infections caused by Gram-positive microorganisms such as methicillin-resistant staphylococci and enterococci including vancomycin-resistant enterococci. A representative compound from a series of glycopeptide derivatives.

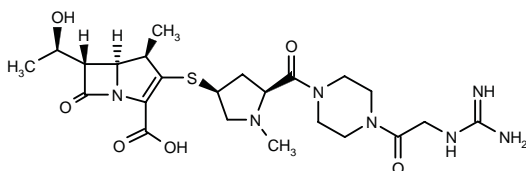
SOURCE – Advanced Medicine.

REFERENCES

1. Christensen, B.G. et al. (Advanced Medicine, Inc.) *Glycopeptide derivs.* WO 0157071.

308607

(1*R*,5*S*,6*S*)-2-[5(*S*)-[4-(2-Guanidinoacetyl)piperazin-1-ylcarbonyl]-1-methylpyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



C23 H35 N7 O6 S; Mol wt: 537.6385

ACTION – A representative compound from a series of 1-methylcarbapenem derivatives with antibacterial activity. This compound displayed MIC values of 0.2 µg/ml against *Pseudomonas aeruginosa* and < 0.01 µg/ml against *Staphylococcus aureus* and *Escherichia coli* strains. Following s.c. administration to mice, it gave ED₅₀ values of 0.184, 1.00 and 0.915 mg/kg, respectively, against the above-mentioned bacteria. Studies in different animal species demonstrated its safety and adequate pharmacokinetic profile.

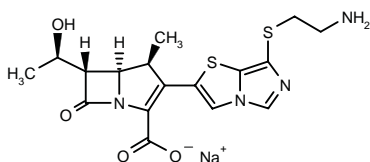
SOURCE – Sankyo.

REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *1-Methylcarbapenem cpds.* JP 2001288186, WO 0157041.

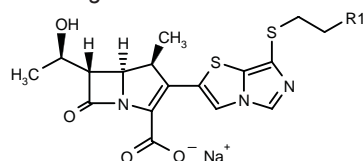
308612

(1*S*,5*R*,6*S*)-2-[7-(2-Aminoethylsulfanyl)imidazo[5,1-*b*]-thiazol-2-yl]-6-[1(*R*)-hydroxyethyl]-1-methyl-carbapen-2-em-3-carboxylic acid sodium salt



C17 H19 N4 Na O4 S2; Mol wt: 430.4831

ACTION – Carbapenem antibacterial agent with potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), influenza viruses and β-lactamase-producing bacteria, reported to display high stability to dehydropeptidase type I (DHP-I). *In vitro*, compound exhibited MIC values of < 0.025, 1.56, < 0.025, 0.20, 0.05, 0.05, 0.10 and 0.10 µg/ml, respectively, when tested against *S. aureus* 209P JC-1, MRSA M126, *Staphylococcus epidermidis* ATCC14990, *Enterococcus faecalis* w-73, PRSP PRC9, *Haemophilus influenzae* PRC2, *Escherichia coli* NIHJ JC-2 and *Klebsiella pneumoniae* PC1602. No mortality was observed following administration of 2000 mg/kg i.v. to mice. Other exemplified compounds from this series of carbapenem derivatives include the following:



Compound	R1	Formula
308613	F	C ₁₇ H ₁₇ FN ₃ NaO ₄ S ₂
308614	NHC(=NH)NH ₂	C ₁₈ H ₂₁ N ₆ NaO ₄ S ₂

SOURCE – Meiji Seika.

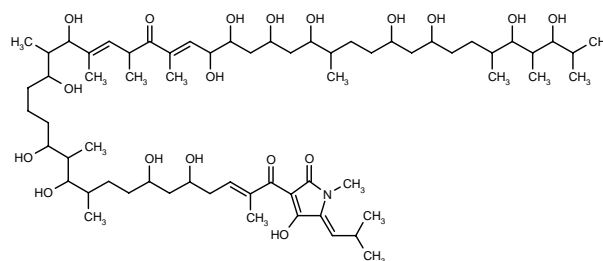
REFERENCES

1. Kano, Y. et al. (Meiji Seika Kaisha, Ltd.) *Novel carbapenem derivs.* WO 0155154.

AMYCOMYCIN

307454

5,7,11,13,17,19,26,27,29,31,35,37,41,43-Tetradecahydroxy-1-[(5*Z*)-4-hydroxy-1-methyl-5-(2-methylpropylidene)-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]-2,10,12,18,20,22,24,32,40,42,44-undecamethyl-2(*E*),20(*E*),24(*E*)-pentatetracontatriene-1,23-dione



C65 H115 N O18; Mol wt: 1198.6130

ACTION – Antibiotic isolated from a culture of *Amycolatopsis* sp. ST101170 (DSM 12216), with good antibacterial activity, particularly against Gram-positive bacteria. It exhibited superior activity to vancomycin against a wide series of bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis* and vancomycin- or teicoplanin-resistant strains such as *Enterococcus faecalis*, *Enterococcus faecium* or *Enterococcus gallinarum*.

SOURCE – Aventis Pharma.

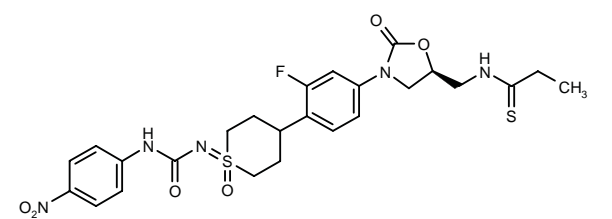
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ANTIBACTERIAL DRUGS

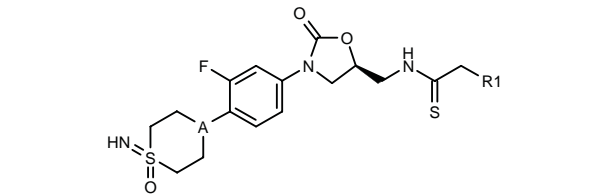
307528

N-[3-[3-Fluoro-4-[(Z)-1-[N-(4-nitrophenyl)carbamoyl-imino]-1-oxotetrahydrothiopyran-4-yl]phenyl]-2-oxoxazolidin-5(S)-ylmethyl]propanethioamide



C25 H28 F N5 O6 S2; Mol wt: 577.6552

ACTION – Oxazolidinone antibacterial agent with potent activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 9213 (MIC = 0.5 µg/ml), *Staphylococcus epidermidis* 30593 (MIC = 0.25 µg/ml), *Enterococcus faecium* 12712 (MIC = 0.25 µg/ml), *Streptococcus pneumoniae* 9912 (MIC < 0.06 µg/ml), *Streptococcus pyogenes* 152 (MIC = 0.125 µg/ml), *Enterococcus faecalis* 9217 (MIC = 0.25 µg/ml) and *Moraxella catarrhalis* 30607 (MIC = 0.25 µg/ml). Within this series of oxazolidinones having a sulfoximine functionality, the following are also included:



Compound	R1	A	Formula
307543	Me	N	C ₁₇ H ₂₂ FN ₃ O ₄ S
307545	H	CH	C ₁₇ H ₂₂ FN ₃ O ₃ S ₂

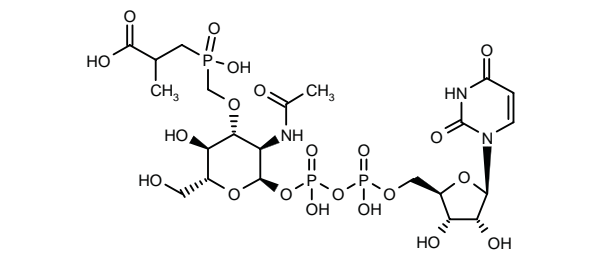
SOURCE – Pharmacia.

REFERENCES

1. Hester, J.B. Jr. and Alexander, D.L. (Pharmacia Corp.) *Oxazolidinones having a sulfoximine functionality and their use as antimicrobial agents*. WO 0146185.

307646

P¹-[2-Acetamido-3-O-[(2-carboxypropyl)(hydroxy)-phosphorylmethyl]-2-deoxy-α-D-glucopyranosyl]-P²-(uridin-5'-yl)diphosphate



C22 H36 N3 O21 P3; Mol wt: 771.4484

ACTION – Antibacterial agent, a potent inhibitor of the *Escherichia coli* cell wall L-alanine-adding enzyme (MurC; IC₅₀ = 49 nM).

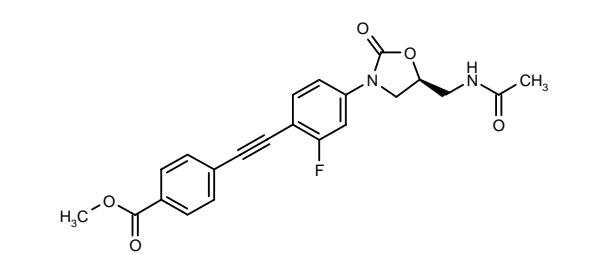
SOURCE – AstraZeneca.

REFERENCES

1. Reck, F. et al. *Inhibitors of the bacterial cell wall biosynthesis enzyme MurC*. Bioorg Med Chem Lett 2001, 11(11): 1451.

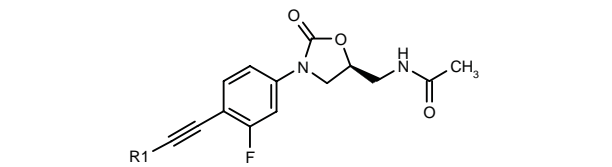
308071

4-[2-[4-[5(S)-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl]ethynyl]benzoic acid methyl ester



C22 H19 F N2 O5; Mol wt: 410.3991

ACTION – Oxazolidinone antibacterial agent, potentially useful for the treatment of a variety of conditions including bacterial infections, psoriasis, arthritis and chemotherapy-induced toxicity. Other specifically claimed compounds are:



Compound	R1	Formula
308072	2-pyrrolyl	C ₁₈ H ₁₆ FN ₃ O ₃
308073	4-(CH2OH)-Ph	C ₂₁ H ₁₉ FN ₂ O ₄
308074	4-MeO-3-Pyr	C ₂₀ H ₁₈ FN ₃ O ₄
308075	3-NH2-Ph	C ₂₀ H ₁₈ FN ₃ O ₃
308076	3-(CO2Me)-Ph	C ₂₂ H ₁₈ FN ₂ O ₅
308077	3-AcNH-Ph	C ₂₂ H ₂₀ FN ₃ O ₄
308078	3-(NH2CH2)-Ph	C ₂₁ H ₂₀ FN ₃ O ₃
308079	4-OH-Ph	C ₂₀ H ₁₇ FN ₂ O ₄

SOURCE – Abbott.

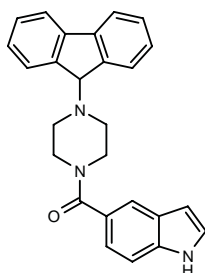
REFERENCES

1. Sciotti, R.J. et al. (Abbott Laboratories Inc.) *Oxazolidinone chemotherapeutic agents*. US 6277868.

ANTIMYCOBACTERIAL AGENTS

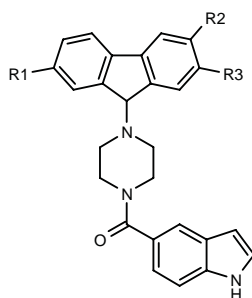
308282

1-[4-(9*H*-Fluoren-9-yl)piperazin-1-yl]-1-(1*H*-indol-5-yl)-methanone



C26 H23 N3 O; Mol wt: 393.4877

ACTION – Antimycobacterial agent for use in the treatment of tuberculosis that acts by inhibiting mycobacterial enoyl-ACP reductase (InhA), and thus interferes with bacterial cell wall biosynthesis. It displayed an IC₅₀ of 0.16-0.34 μM against InhA, and inhibited the growth of the Bacillus-Calmette Guerin strain of *Mycobacterium bovis* with an IC₅₀ of 8.3 μM. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
308283	NO2	H	H	C ₂₆ H ₂₂ N ₄ O ₃
308284	H	NO2	H	C ₂₆ H ₂₂ N ₄ O ₃
308285	Br	H	Br	C ₂₆ H ₂₁ Br ₂ N ₃ O

SOURCE – Genzyme General.

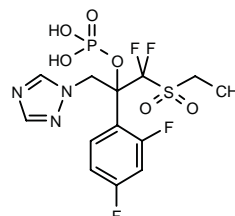
REFERENCES

1. Staveski, M.M. et al. (Genzyme Corp.) *InhA inhibitors and methods of use thereof*. WO 0156974.

ANTIFUNGAL AGENTS

307124

(+)-1-(2,4-Difluorophenyl)-2-(ethylsulfonyl)-2,2-difluoro-1-(1*H*-1,2,4-triazol-1-ylmethyl)ethyl dihydrogen phosphate



C13 H14 F4 N3 O6 P S; Mol wt: 447.3006

ACTION – Phosphorylated azole antifungal agent with equivalent potency to the nonphosphorylated parent compound* against *Candida albicans* infection in mice and improved water solubility (4.80 mg/ml vs. 0.50 mg/ml for the parent compound).

SOURCE – SSP.

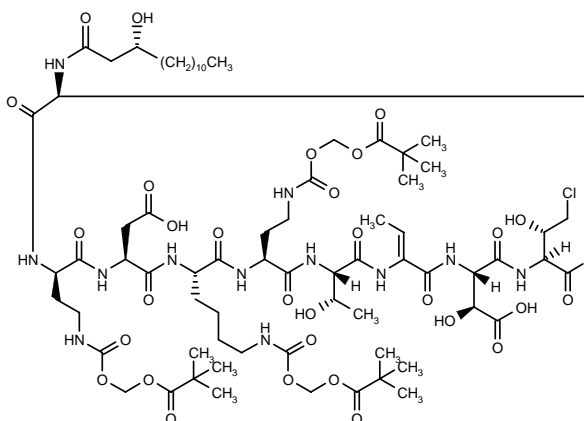
REFERENCES

1. Tokizawa, M. et al. (SSP Co., Ltd.) *Azole derivs. or their salts*. JP 2001163892.

*See **SS-750** Drug Data Rep 2000, 22(11): 1013.

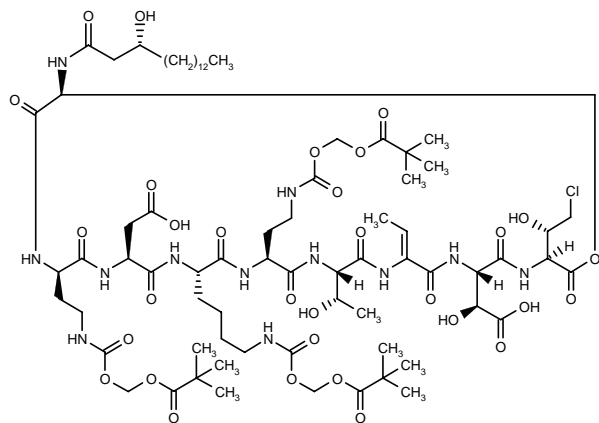
307792

N-[3(*R*)-Hydroxytetradecanoyl]-*L*-seryl-*N*⁴-(*tert*-butylcarbonyloxymethoxycarbonyl)-*D*-(2,4-diaminobutyl)-*L*-aspartyl-*N*⁶-(*tert*-butylcarbonyloxymethoxycarbonyl)-*L*-lysyl-*N*⁴-(*tert*-butylcarbonyloxymethoxycarbonyl)-*L*-(2,4-diaminobutyl)-*L*-allothreonyl-(*Z*)-2,3-didehydro-2-aminobutyl-3(*S*)-hydroxy-*L*-aspartyl-4-chloro-*L*-threonine C-1.9-*O*-3.1-lactone



C72 H117 Cl N12 O31; Mol wt: 1682.2220

ACTION – Antifungal agent, an *N*-acycloxymethyl carbamate linked prodrug of pseudomycin with good *in vivo* activity in a model of systemic candidiasis in mice (ED₅₀ = 6.4-14.1 mg/kg i.p. x 4). *In vitro* bioactivation studies showed that this prodrug was capable of generating sufficient amounts of parent drug. Moreover, compound, unlike pseudomycin, did not induce tail vein toxicity in mice and was devoid of systemic toxicity at up to 75 mg/kg. Another related compound is:



307793: C74 H121 Cl N12 O31

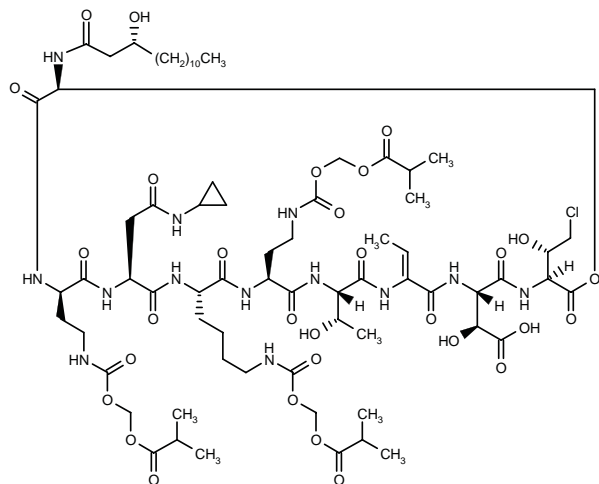
SOURCE – Lilly.

REFERENCES

1. Chen, S.H. et al. (Eli Lilly and Company) *Pseudomycin prodrugs*. WO 0105813.
2. Sun, X. et al. *N-Acyloxymethyl carbamate linked prodrugs of pseudomycins are novel antifungal agents*. Bioorg Med Chem Lett 2001, 11(14): 1875.

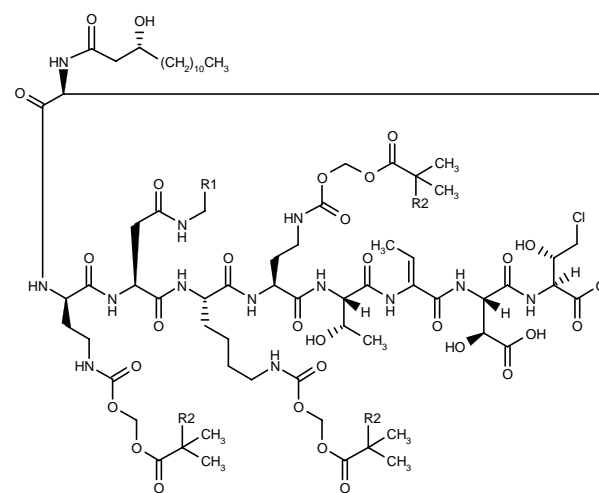
307829

N-[3(*R*)-Hydroxytetradecanoyl]-*L*-seryl-*N*⁴-(isopropylcarbonyloxymethoxycarbonyl)-*D*-(2,4-diaminobutyl)-*N*⁴-(cyclopropyl)-*L*-asparaginyl-*N*⁴-(isopropylcarbonyloxymethoxycarbonyl)-*L*-lysyl-*N*⁴-(isopropylcarbonyloxymethoxycarbonyl)-*L*-(2,4-diaminobutyl)-*L*-allothreonyl-(*Z*)-2,3-didehydro-2-aminobutyl-3(*S*)-hydroxy-*L*-aspartyl-4-chloro-*L*-threonine *C*-1.9-*O*-3.1-lactone



C72 H116 Cl N13 O30; Mol wt: 1679.2220

ACTION – Antifungal agent, an *N*-acylated prodrug of 3-amidopseudomycin B with excellent *in vivo* efficacy against murine candidiasis (ED₅₀ < 5.0 mg/kg i.p.) and cryptococcosis (ED₅₀ = 0.56 mg/kg i.p.). Compound was well tolerated in mice up to 125 mg/kg i.v. Other related prodrugs are:



Compound	R1	R2	Formula
307834	CH2N(Me)2	H	C ₇₃ H ₁₂₁ ClN ₁₄ O ₃₀
307835	CO2Me	H	C ₇₂ H ₁₁₆ ClN ₁₃ O ₃₂
307838	CO2Me	Me	C ₇₅ H ₁₂₂ ClN ₁₃ O ₃₂

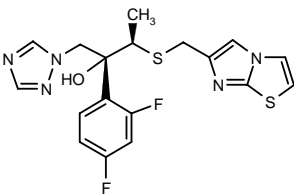
SOURCE – Lilly.

REFERENCES

1. Chen, S.H. et al. (Eli Lilly and Company). *Pseudomucin prodrugs*. WO 0105813.
2. Sun, X. et al. *Prodrugs of 3-amido bearing pseudomycin analogues: Novel antifungal agents*. Bioorg Med Chem Lett 2001, 11(14): 1881.

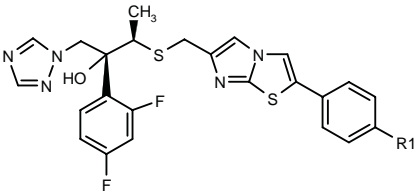
308685

2(*R*)-(2,4-Difluorophenyl)-3(*R*)-(imidazo[2,1-*b*]thiazol-6-ylmethylsulfanyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol

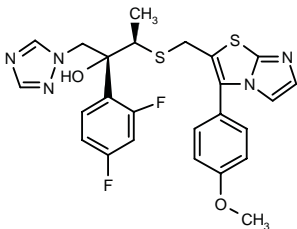


C18 H17 F2 N5 O S2; Mol wt: 421.4943

ACTION – Antifungal agent for use in the treatment of superficial and deep mycoses. *In vitro*, it showed IC₈₀ values of 2, 2 and < 0.0625 µg/ml against *Aspergillus fumigatus* TIMM1775, *Candida albicans* TIMM3163 and *C. albicans* TIMM1768, respectively. *In vivo*, this compound demonstrated better antifungal activity than fluconazole following p.o. administration (5 mg/kg) to mice infected with *C. albicans* TIMM1768. Other triazole derivatives are:



Compound	R1	Formula
308686	OMe	C ₂₅ H ₂₃ F ₂ N ₅ O ₂ S ₂
308687	F	C ₂₄ H ₂₀ F ₃ N ₅ OS ₂
308688	Cl	C ₂₄ H ₂₀ ClF ₂ N ₅ OS ₂



308689: C25 H23 F2 N5 O2 S2

SOURCE – Meiji Seika.

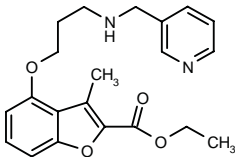
REFERENCES

1. Umemura, E. et al. (Meiji Seika Kaisha, Ltd.) *Novel triazole derivs. and antifungal agnets containing them.* JP 2001192386.

RO-09-4609

307790

3-Methyl-4-[3-(pyridin-3-ylmethylamino)propoxy]-1-benzofuran-2-carboxylic acid ethyl ester



C21 H24 N2 O4; Mol wt: 368.4306

ACTION – Antifungal agent, an inhibitor of *Candida albicans* N-myristoyltransferase (IC₅₀ = 0.1 μM) with very high selectivity over human enzyme (C₅₀ > 540 μM). It exerted moderate *in vitro* antifungal activity against *C. albicans* (IC₅₀ = 1.6 μM) and was inactive *in vivo* in a systemic candidiasis model in mice. Considered a useful lead compound for further optimization.

SOURCE – Roche.

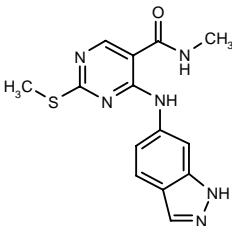
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1. Aoki, Y. et al. (F. Hoffmann-La Roche AG) *Novel bicyclic cpds.* WO 0037464.
2. Masubuchi, M. et al. *Design and synthesis of novel benzofurans as a new class of antifungal agents targeting fungal N-myristoyltransferase. Part 1.* Bioorg Med Chem Lett 2001, 11(14): 1833.

ANTIVIRAL DRUGS

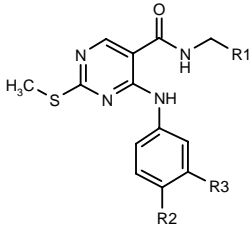
305632

4-(1*H*-Indazol-6-ylamino)-*N*-methyl-2-(methylsulfanyl)-pyrimidine-5-carboxamide



C14 H14 N6 O S; Mol wt: 314.3716

ACTION – Antiviral agent able to inhibit the proliferation of hepatitis B virus (HBV) and HIV by inhibiting reverse transcriptase (RT; 77 and 42% inhibition of HBV RT and HIV RT, respectively, at 0.1 μg/ml). In addition, it was shown to inhibit HBV RT in the HBV-producing HepG 2.2.15 cell line (70% inhibition at 0.1 μg/ml). No cytotoxicity was detected in HepG2 cells (CC₅₀ > 100 μg/ml), nor was any acute toxicity observed in rats (LD₅₀ > 4 g/kg p.o.). Other compounds from this series of 5-pyrimidinecarboxamide derivatives include the following:



Compound	R1	R2,R3	Formula
305633	H	-NHN=CH-	C ₁₄ H ₁₄ N ₆ OS
305635	CH2OH	-CH=NNH-	C ₁₅ H ₁₆ N ₆ O ₂ S

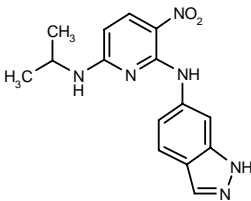
SOURCE – Dong-Wha.

REFERENCES

1. Yoon, S.J. et al. (Dong-Wha Pharmaceuticals Industry Co. Ltd) *Novel 5-pyrimidinecarboxamide derivs. and the pharmaceutical compsns. containing said derivs.* WO 0138308.

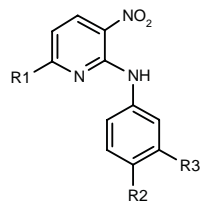
305636

*N*²-(1*H*-Indazol-6-yl)-*N*⁶-isopropyl-3-nitropyridine-2,6-diamine



C15 H16 N6 O2; Mol wt: 312.3314

ACTION – Antiviral agent able to inhibit the proliferation of hepatitis B virus (HBV) and HIV by inhibiting reverse transcriptase (RT; 76 and 50% inhibition of HBV RT and HIV RT, respectively, at 0.1 μg/ml). In addition, it was shown to inhibit HBV RT in the HBV-producing HepG 2.2.15 cell line (72% inhibition at 0.1 μg/ml). No cytotoxicity was detected in HepG2 cells (CC₅₀ > 100 μg/ml), nor was any acute toxicity observed in rats (LD₅₀ > 2 g/kg p.o.). Other compounds from this series of 3-nitropyridine derivatives include the following:



Compound	R1	R2,R3	Formula
305638	OMe	-CH=NNH-	C ₁₃ H ₁₁ N ₅ O ₃
305639	N(Et)CH ₂ CH ₂ OH	-NHN=CH-	C ₁₆ H ₁₈ N ₆ O ₃

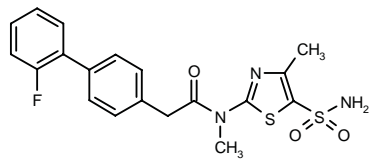
SOURCE – Dong-Wha.

REFERENCES

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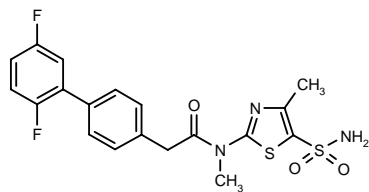
307732

2-(2'-Fluorobiphenyl-4-yl)-N-methyl-N-(4-methyl-5-sulfamoylthiazol-2-yl)acetamide



C19 H18 F N3 O3 S2; Mol wt: 419.4992

ACTION – Antiviral agent for the treatment of infections caused by herpesviruses, particularly herpes simplex virus (HSV), with IC₅₀ values of < 0.01 and < 0.01 μM against HSV-1 F/Vero and HSV-2 G/Vero strains, respectively, compared to IC₅₀ values of 1 and 3 μM, respectively, for aciclovir. Compound also exhibited antiviral activity *in vivo* in HSV-2-infected mice (ED₅₀ = 0.7 mg/kg p.o. t.i.d. x 5 days). Another specifically claimed compound from this series of thiazolyl amide derivatives is:



307733: C19 H17 F2 N3 O3 S2

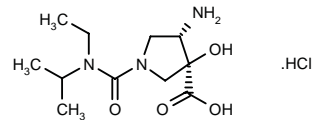
SOURCE – Bayer.

REFERENCES

1. Fischer, R. et al. (Bayer AG) *Thiazolyl amide derivs.* DE 19962532, WO 0147904.

308266

(3*S**,4*S**)-4-Amino-1-(*N*-ethyl-*N*-isopropylcarbamoyl)-3-hydroxypyrrolidine-3-carboxylic acid hydrochloride



C11 H21 N3 O4 . HCl; Mol wt: 295.7648

ACTION – Influenza A virus neuraminidase inhibitor (K_i = 0.36 μM against A/N2 strain) with substantially less activity against influenza B enzyme (K_i = 210 μM). Compound inhibited the replication of influenza A/Victoria/3/75 (H3N2) with an EC₅₀ of 2.0 μM and was less active against influenza B/Hong Kong/5/72 (EC₅₀ = 305 μM). No detectable cytotoxicity was seen up to 1 mM.

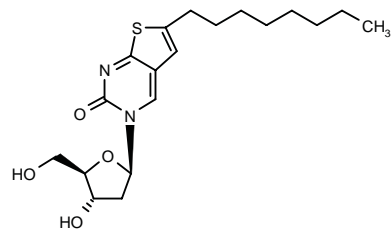
SOURCE – Abbott.

REFERENCES

1. Kati, W.M. et al. *Novel alpha- and beta-amino acid inhibitors of influenza virus neuraminidase.* Antimicrob Agents Chemother 2001, 45(9): 2563.

308572

3-(2-Deoxy-β-D-ribofuranosyl)-6-octylthieno[2,3-*d*]pyrimidin-2(3*H*)-one



C19 H28 N2 O4 S; Mol wt: 380.5062

ACTION – Antiviral agent active against varicella-zoster virus (VZV; IC₅₀ = 2-5 nM) and inactive against thymidine kinase-deficient VZV strains, herpes simplex virus type 1 and 2 (HSV-1, HSV-2), and cytomegalovirus. No cytotoxicity was seen at pharmacologically active concentrations.

SOURCES – Cardiff University, Cardiff (GB); CNRS; Rega Institute for Medical Research, Leuven (BE).

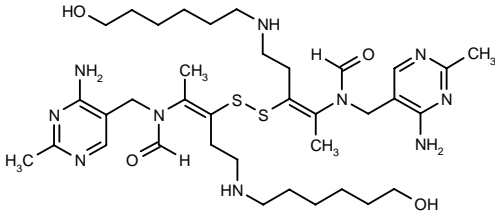
REFERENCES

1. Brancale, A. et al. *Bicyclic anti-VZV nucleosides: Thieno analogues retain full antiviral activity.* Bioorg Med Chem Lett 2001, 11(18): 2507.

AIDS MEDICINES

305454

Bis[2-[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)-*N*-formylamino]-1-[2-(6-hydroxyhexylamino)ethyl]-1-propenyl]disulfide



C36 H60 N10 O4 S2; Mol wt: 761.0680

ACTION – Antiviral agent for AIDS, a representative compound from a series of thiamine disulfide derivatives with good water solubility compared to previously disclosed thiamine disulfides. *In vitro*, compound exhibited concentration-dependent (12.5-100 μM) inhibition of HIV-1 activity in HeLa cells.

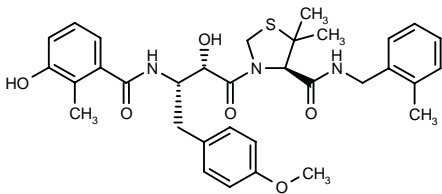
SOURCE – Nissui.

REFERENCES

1. Shoji, S. and Tachibana, K. (Nissui Pharmaceutical Co. Ltd.) *Thiamin disulfide derivs.* JP 2001139557, WO 0136391.

307404

3-[2(*S*)-Hydroxy-3(*S*)-(3-hydroxy-2-methylbenzamido)-4-(4-methoxyphenyl)butyryl]-5,5-dimethyl-*N*-(2-methylbenzyl)thiazolidine-4(*R*)-carboxamide



C33 H39 N3 O6 S; Mol wt: 605.7521

ACTION – Dipeptide compound from a series of HIV protease inhibitors with potential in the treatment of AIDS. The compound inhibited HIV-1 protease by 95% at 50 nM and displayed potent antiviral activity in HIV-infected CEM-SS cells. Following intraduodenal administration to rats (10 mg/kg), a plasma concentration of 0.42 μg/ml was reached after 30 min.

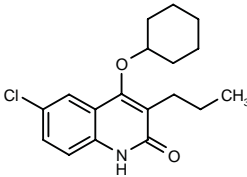
SOURCE – Japan Energy.

REFERENCES

1. Mimoto, T. et al. (Japan Energy Corp.) *Novel dipeptide cpd. and medicinal use thereof.* WO 0147948.

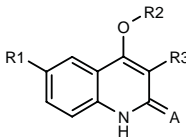
307536

6-Chloro-4-(cyclohexyloxy)-3-propylquinolin-2(1*H*)-one



C18 H22 Cl N O2; Mol wt: 319.8298

ACTION – Antiviral agent for the prevention and treatment of retrovirus-mediated infections, particularly AIDS. The compound showed an IC₅₀ below 0.1 μM *in vitro* in HIV-infected MT-4 cells. Other exemplified quinolone derivatives are:



Compound	R1	R2	R3	A	Formula
307537	Cl	cyclohexyl	i-Pr	O	C ₁₈ H ₂₂ ClNO ₂
307538	Cl	cyclohexyl	Pr	S	C ₁₈ H ₂₂ ClNOS
307539	Cl	cyclopropyl-ethynylene	Pr	O	C ₁₇ H ₁₆ ClNO ₂
307540	F	cyclopropyl-ethynylene	Pr	O	C ₁₇ H ₁₆ FNO ₂
307541	F	cyclopropyl-ethynylene	Et	O	C ₁₆ H ₁₄ FNO ₂
307542	Cl	cyclopropyl-ethynylene	i-Pr	O	C ₁₇ H ₁₆ ClNO ₂
307544	F	cyclopropyl-ethynylene	i-Bu	O	C ₁₈ H ₁₈ FNO ₂
307546	F	cyclopropyl-ethynylene	i-Pr	O	C ₁₇ H ₁₆ FNO ₂

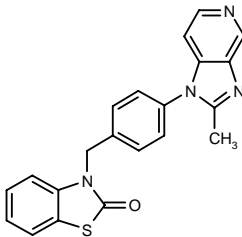
SOURCE – GlaxoSmithKline.

REFERENCES

1. Andrews, C.W. III et al. (Glaxo Group Ltd.) *Quinolone cpds. for use in treating viral infections.* WO 0146150.

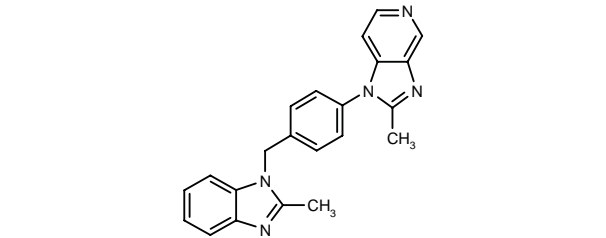
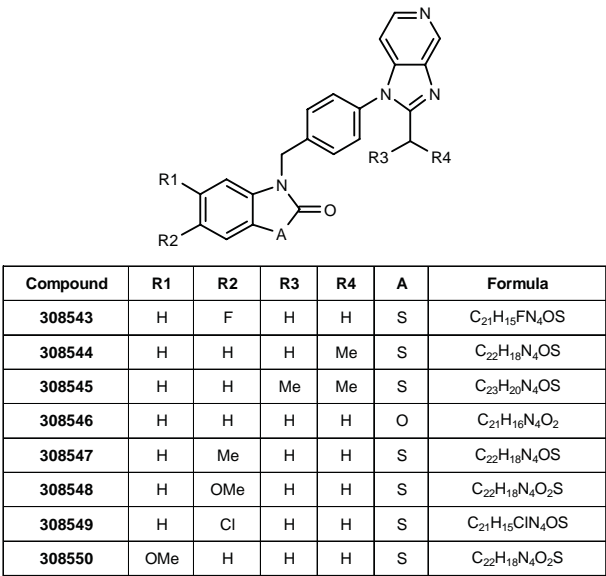
308542

3-[4-(2-Methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)benzyl]-benzothiazol-2(3*H*)-one



C21 H16 N4 O S; Mol wt: 372.4504

ACTION – HIV reverse transcriptase inhibitor (78% inhibition at 10 μM) that is expected to be useful for the treatment of AIDS. Other exemplified imidazo[4,5-*c*]pyridine derivatives include the following:



308551: C22 H19 N5

SOURCE – Pfizer.

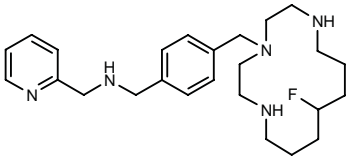
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AMD-8897

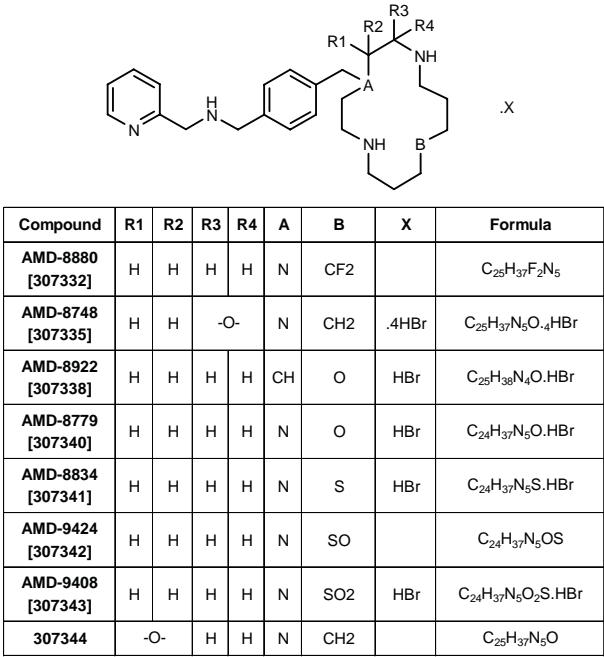
307330

N-[4-(11-Fluoro-1,4,7-triazacyclotetradecan-4-ylmethyl)-benzyl]-*N*-(pyridin-2-ylmethyl)amine



C25 H38 F N5; Mol wt: 427.6082

ACTION – Agent that binds to chemokine receptors including CXCR4 and CCR5, expected to be useful as an antiviral agent, as well as for the treatment of other disorders involving chemokine receptors such as arthritis, multiple sclerosis, asthma and cancer. Compound gave > 50% inhibition of SDF-1 α -induced calcium flux in SUP-T1 cells at a concentration of 25 μ g/ml and is reported to inhibit HIV-1 NL4.3 replication in MT-4 cells with an EC₅₀ value in the range 0.003-33.3 μ g/ml. Other exemplified compounds from this series of monocyclic polyamine derivatives are:



SOURCE – AnorMED.

REFERENCES

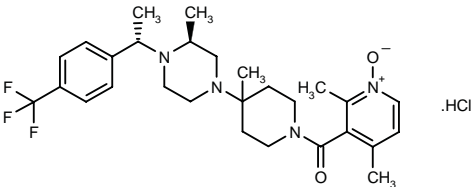
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SCH-350634

309107

4-[1-(2,4-Dimethyl-1-oxidopyridin-3-ylcarbonyl)-4-methyl-piperidin-4-yl]-2(*S*)-methyl-1-[1(*S*)-[4-(trifluoromethyl)-phenyl]ethyl]piperazine hydrochloride

2,4-Dimethyl-3-[4-methyl-4-[3(*S*)-methyl-4-[1(*S*)-[4-(trifluoromethyl)phenyl]ethyl]-1-piperazinyl]piperidin-1-ylcarbonyl]pyridine *N*-oxide hydrochloride



C28 H37 F3 N4 O2 . HCl; Mol wt: 555.0812

ACTION – Anti-HIV agent, a piperazine-based CCR5 antagonist with high affinity for the CCR5 receptor (K_i = 7 nM), 30-50-fold selectivity over muscarinic M₁ and M₂ receptors (K_i = 350 nM and 250 nM, respectively) and negligible activity at other receptors. Compound inhibited HIV-1 entry into U-87 cells (IC₅₀ = 1.0 nM) and the replication of HIV-1 isolates in peripheral blood mononuclear cells (PBMCs; IC₅₀ = 2-20 nM). It exhibited high oral bioavailability in rats, dogs (65%) and monkeys (59%).

SOURCE – Schering-Plough.

REFERENCES

1. Baroudy, B.M. et al. (Schering Corp.) *Piperazine derivs. useful as CCR5 antagonists*. WO 0066558.

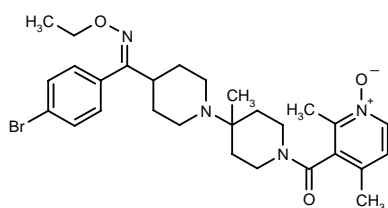
2. Tagat, J.R. et al. *Piperazine-based CCR5 antagonists as HIV-1 inhibitors. II. Discovery of 1-[(2,4-dimethyl-3-pyridinyl)carbonyl]-4-methyl-4-[3(S)-methyl-4[1(S)-[4-(trifluoromethyl)phenyl]ethyl]-1-piperazinyl]-piperidine N1-oxide (Sch-350634), an orally bioavailable, potent CCR5 antagonist*. J Med Chem 2001, 44(21): 3343.

SCH-351125

305456

(Z)-1-(4-Bromophenyl)-1-[1'-(2,4-dimethyl-1-oxidopyridin-3-ylcarbonyl)-4'-methyl-1,4'-bipiperidin-4-yl]methanone O-ethyloxime

SCH-C
Schering C



C28 H37 Br N4 O3; Mol wt: 557.5293

ACTION – Anti-HIV agent, an antagonist of human chemokine CCR5 receptors, with a K_i of 2.1 nM and little or no effect at other chemokine receptors or muscarinic receptors at concentrations of 2 μ M or more. Compound inhibited HIV-1 entry (IC_{50} = 0.6 nM) and HIV-1 replication (IC_{50} = 2 nM) in peripheral blood mononuclear cells (PBMCs) infected with M-tropic HIV-1 isolates, and showed low cytotoxicity in PBMC cultures (CC_{50} = 92 μ M). In pharmacokinetic experiments in rats, dogs and monkeys, compound administered as the tartrate salt showed high oral bioavailability (63, 52 and 92%, respectively) and absorption, the major route of excretion being the urine in rats and dogs and the bile in monkeys. Currently being evaluated in phase I clinical trials.

SOURCE – Schering-Plough.

REFERENCES

1. Baroudy, B.M. et al. (Schering Corp.) *Piperidine derivs. useful as CCR5 antagonists*. WO 0066559.

2. Baroudy, B.M. *A small molecule antagonist of CCR5 that effectively inhibits HIV-1 potential as a novel antiretroviral agent*. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb2, San Francisco) 2000, Abst S17.

3. Baroudy, B.M. *Second generation CCR5 antagonist that inhibits HIV-1 entry*. 1st IAS Conf HIV Pathog Treat (July 8-11, Buenos Aires) 2001, Abst 70.

4. Moore, J. *HIV-1 escape from small molecule CCR5 inhibitors in PBMC does not involve co-receptor switching to CXCR4 use*. 1st IAS Conf HIV Pathog Treat (July 8-11, Buenos Aires) 2001, Abst LB-O5.

5. Palani, A. et al. *Discovery of 4-[(Z)-(4-bromophenyl)-(ethoxyimino)methyl]-1'-[(2,4-dimethyl-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidine N-oxide (SCH 351125). An orally bioavailable human CCR5 antagonist for the treatment of HIV infection*. J Med Chem 2001, 44(21): 3339.

6. Reyes, G. et al. *Development of CCR5 antagonists as a new class of anti-HIV therapeutic*. 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst L11.

7. Strizki, J. *Development of SCH, a small molecule antagonist of CCR5, as a novel HIV therapeutic*. Antivir Res 2001, 51(1, Special Issue): Abst 010.

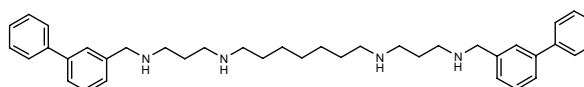
8. Strizki, J.M. et al. *SCH-C (SCH 351125), an orally bioavailable, small molecule antagonist of the chemokine receptor CCR5, is a potent inhibitor of HIV-1 infection in vitro and in vivo*. Proc Natl Acad Sci USA 2001, 98(22): 12718.

9. Tremblay, C. et al. *SCH-C, a CCR5 antagonist, has synergistic interactions with antiretrovirals from various classes*. 1st IAS Conf HIV Pathog Treat (July 8-11, Buenos Aires) 2001, Abst 245.

TREATMENT OF PROTOZOAL DISEASES

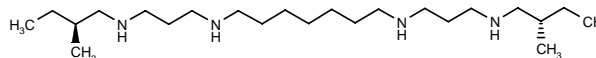
307654

N,N'-Bis[3-(biphenyl-3-ylmethylamino)propyl]heptane-1,7-diamine



C39 H52 N4; Mol wt: 576.8678

ACTION – Antiprotozoal agent, an alkylpolyamine analogue active against *Trypanosoma brucei* *in vitro* (IC_{50} = 0.24 μ M) and *Encephalitozoon cuniculi* both *in vitro* (IC_{50} = 0.47 μ M) and *in vivo*, where it was curative at doses of 1 and 5 mg/kg i.p. Another related compound is:



307655: C23 H52 N4

SOURCES – Albert Einstein College of Medicine, New York, NY (US); Johns Hopkins University, Baltimore, MD (US); Pace University, New York, NY (US); Wayne State University, Detroit, MI (US).

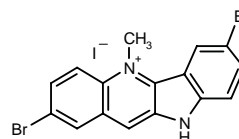
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2,7-DIBROMOCRYPTOLEPINE

307414

2,7-Dibromo-5-methyl-10*H*-indolo[3,2-*b*]quinolin-5-ium iodide



C16 H11 Br2 I N2 ; Mol wt: 517.9849

ACTION – Antimalarial agent, a cryptolepine analogue with potent *in vitro* activity against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum* (IC_{50} = 0.026 and 0.049 μ M, respectively). Compound inhibited β -hematin formation *in vitro*. In *Plasmodium berghei*-infected mice, a dose of 12.5 mg/kg i.p. for 4 days suppressed parasitemia by 89%, activity comparable to that of chloroquine, without toxicity.

SOURCES – University of Bradford (GB); London School of Hygiene & Tropical Medicine, London (GB).

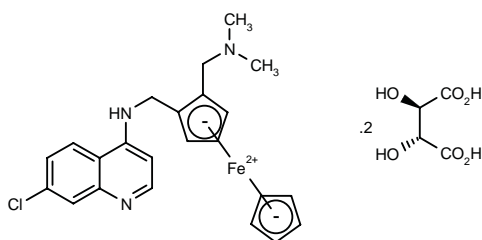
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1. Wright, C.W. et al. *Synthesis and evaluation of cryptolepine analogues for their potential as new antimalarial agents*. J Med Chem 2001, 44(19): 3187.

FERROCHLOROQUINE

307848

3-(7-Chloroquinolin-4-ylaminomethyl)-4-(dimethylaminomethyl)ferrocene bis(L-tartrate)



C23 H24 Cl Fe N3 . 2C4 H6 O6; Mol wt: 733.9324

ACTION – Antimalarial agent, an organometal chloroquine analogue proven to be active *in vitro* against Gabonese isolates of *Plasmodium falciparum*, 95% of which were resistant to chloroquine. Compound showed IC₅₀ values of 0.43-30.9 nM (geometric mean IC₅₀ = 10.8 nM) and was more active than chloroquine (IC₅₀ = 370 nM), quinine (IC₅₀ = 341 nM), amodiaquine (IC₅₀ = 18.1 nM) and primaquine (IC₅₀ = 7600 nM), but less potent than mefloquine (IC₅₀ = 8.3 nM), halofantrine (IC₅₀ = 0.8 nM), atovaquone (IC₅₀ = 3.3 nM) and artesunate (IC₅₀ = 2.9 nM).

SOURCE – Pierre Fabre (bioMerieux-Pierre Fabre).

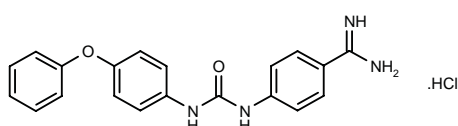
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3. Pradines, B. et al. *Ferrocene-chloroquine analogues as antimalarial agents: In vitro activity of ferrochloroquine against 103 Gabonese isolates of Plasmodium falciparum*. J Antimicrob Chemother 2001, 48(2): 179.

WR-268961

308264

4-[3-(4-Phenoxyphenyl)ureido]benzenecarboxamide hydrochloride



C20 H18 N4 O2 . HCl; Mol wt: 382.8491

ACTION – Antimalarial agent, a small nonpeptide compound with relatively high solubility in water that inhibits the growth of *Plasmodium falciparum* with IC₅₀ values ranging from 0.03 µg/ml against the chloroquine-resistant W2 strain to 0.16 µg/ml against the chloroquine-sensitive D6 strain. Compound targets plasmepsins, aspartic proteases which are critical for hemoglobin degradation during the intraerythrocytic stage (K_i = 1.2-6.1 µM), and showed high selectivity over mammalian proteases such as human cathepsin D.

SOURCES – University of Florida, Gainesville, FL (US); Walter Reed Army Institute, Washington, DC (US).

REFERENCES

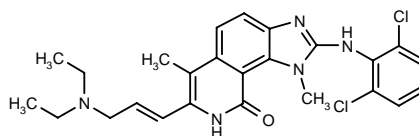
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2. Kam, C.-M. et al. *Mammalian tissue trypsin-like enzymes: Substrate specificity and inhibitory potency of substituted isocoumarin mechanism-based inhibitors, benzamidine derivatives, and arginine fluoroalkyl ketone transition-state inhibitors*. Arch Biochem Biophys 1995, 316(2): 808.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

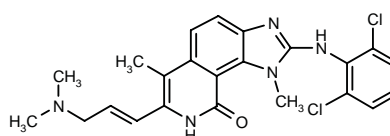
303507

2-(2,6-Dichlorophenylamino)-7-[3-(diethylamino)-1-propenyl]-1,6-dimethyl-8,9-dihydro-1H-imidazo[4,5-h]-isoquinolin-9-one



C25 H27 Cl2 N5 O; Mol wt: 484.4283

ACTION – Potent inhibitor of Lck protein tyrosine kinase (IC₅₀ = 0.5 nM) with selectivity for Src family kinases (IC₅₀ = 0.15 and 1 nM against Src and Lvn, respectively) over other kinases. Compound inhibited anti-CD3 antibody-induced Ca²⁺ influx in Jurkat cells (EC₅₀ = 5 nM) and IL-2 production both *in vitro* (IC₅₀ = 0.130 µM in Jurkat cells) and *in vivo* (ED₅₀ = 4.5 mg/kg in mice), with *in vivo* efficacy comparable to ciclosporin (ED₅₀ = 10 mg/kg). Potentially useful for the treatment of both chronic and acute T-cell-mediated disorders such as rheumatoid arthritis, multiple sclerosis and transplant rejection, as well as delayed hypersensitivity reactions. Another related compound is:



BIRA-802 [308499]: C23 H23 Cl2 N5 O

SOURCES – University of Bradford (GB); London School of Hygiene & Tropical Medicine, London (GB).

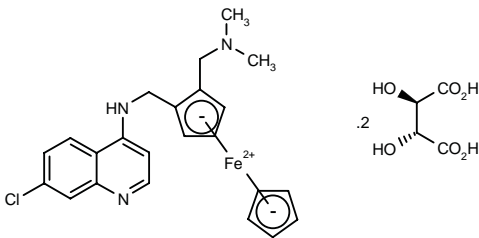
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1. Wright, C.W. et al. *Synthesis and evaluation of cryptolepine analogues for their potential as new antimalarial agents.* J Med Chem 2001, 44(19): 3187.

FERROCHLOROQUINE

307848

3-(7-Chloroquinolin-4-ylaminomethyl)-4-(dimethylamino-methyl)ferrocene bis(L-tartrate)



C23 H24 Cl Fe N3 . 2C4 H6 O6; Mol wt: 733.9324

ACTION – Antimalarial agent, an organometal chloro-quine analogue proven to be active *in vitro* against Gabonese isolates of *Plasmodium falciparum*, 95% of which were resistant to chloroquine. Compound showed IC₅₀ values of 0.43-30.9 nM (geometric mean IC₅₀ = 10.8 nM) and was more active than chloroquine (IC₅₀ = 370 nM), quinine (IC₅₀ = 341 nM), amodiaquine (IC₅₀ = 18.1 nM) and primaquine (IC₅₀ = 7600 nM), but less potent than mefloquine (IC₅₀ = 8.3 nM), halofantrine (IC₅₀ = 0.8 nM), atovaquone (IC₅₀ = 3.3 nM) and artesunate (IC₅₀ = 2.9 nM).

SOURCE – Pierre Fabre (bioMerieux-Pierre Fabre).

REFERENCES

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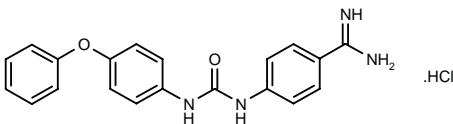
2. Domarle, O. et al. *In vitro antimalarial activity of a new organometallic analog, ferrocene-chloroquine.* Antimicrob Agents Chemother 1998, 42(3): 540.

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WR-268961

308264

4-[3-(4-Phenoxyphenyl)ureido]benzenecarboxamide hydrochloride



C20 H18 N4 O2 . HCl; Mol wt: 382.8491

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SOURCES – University of Florida, Gainesville, FL (US); Walter Reed Army Institute, Washington, DC (US).

REFERENCES

1. Jiang, S. et al. *New class of small nonpeptidyl compounds blocks Plasmodium falciparum development in vitro by inhibiting plasmepsins.* Antimicrob Agents Chemother 2001, 45(9): 2577.

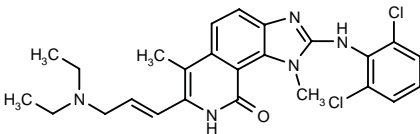
2. Kam, C.-M. et al. *Mammalian tissue trypsin-like enzymes: Substrate specificity and inhibitory potency of substituted isocoumarin mechanism-based inhibitors, benzamidine derivatives, and arginine fluoroalkyl ketone transition-state inhibitors.* Arch Biochem Biophys 1995, 316(2): 808.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

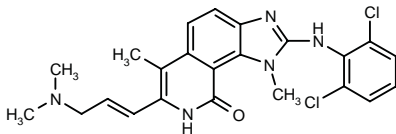
303507

2-(2,6-Dichlorophenylamino)-7-[3-(diethylamino)-1-propenyl]-1,6-dimethyl-8,9-dihydro-1H-imidazo[4,5-*h*]-isoquinolin-9-one



C25 H27 Cl2 N5 O; Mol wt: 484.4283

ACTION – Potent inhibitor of Lck protein tyrosine kinase (IC₅₀ = 0.5 nM) with selectivity for Src family kinases (IC₅₀ = 0.15 and 1 nM against Src and Lvn, respectively) over other kinases. Compound inhibited anti-CD3 antibody-induced Ca²⁺ influx in Jurkat cells (EC₅₀ = 5 nM) and IL-2 production both *in vitro* (IC₅₀ = 0.130 µM in Jurkat cells) and *in vivo* (ED₅₀ = 4.5 mg/kg in mice), with *in vivo* efficacy comparable to ciclosporin (ED₅₀ = 10 mg/kg). Potentially useful for the treatment of both chronic and acute T-cell-mediated disorders such as rheumatoid arthritis, multiple sclerosis and transplant rejection, as well as delayed hypersensitivity reactions. Another related compound is:



BIRA-802 [308499]: C23 H23 Cl2 N5 O

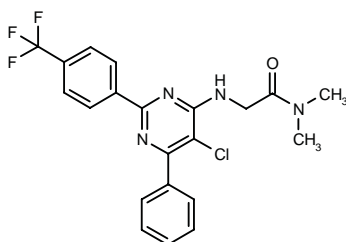
SOURCE – Boehringer Ingelheim.

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2. Goldberg, D. et al. *Discovery of novel and orally active inhibitors of LCK kinase*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 24.
3. Hammach, A. et al. *2-Phenylamino-imidazo[4,5-H]isoquinolin-9-ones novel and highly active inhibitors of LCK kinase*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 265.

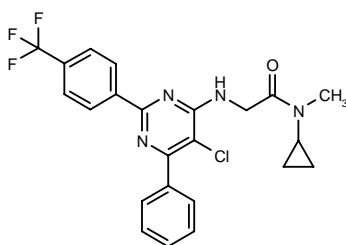
305449

2-[5-Chloro-6-phenyl-2-[4-(trifluoromethyl)phenyl]-pyrimidin-4-ylamino]-*N,N*-dimethylacetamide



C21 H18 Cl F3 N4 O; Mol wt: 434.8472

ACTION – Agent for the treatment of rheumatic diseases such as rheumatoid arthritis, Behçet's disease and ankylosing spondylitis, inflammatory immunological diseases such as multiple sclerosis and systemic lupus erythematosus, and inflammatory autoimmune diseases such as Sjögren's syndrome, proven active against collagen-induced arthritis in mice, giving 96.0% inhibition of arthritis score at day 52 postinduction at 10 mg/kg/day p.o. No effects on ALT or any other signs of toxicity were observed following administration of up to 300 mg/kg/day p.o. x 14 days. Another exemplified compound from this series of [5-chloro-6-phenyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]acetamide derivatives is:



305450: C23 H20 Cl F3 N4 O

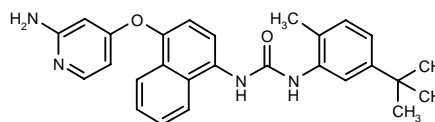
SOURCE – Dainippon Pharmaceutical.

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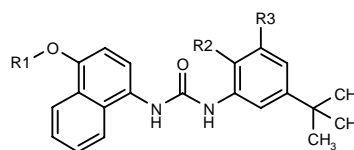
305679

N-[4-(2-Aminopyridin-4-yloxy)naphthalen-1-yl]-*N'*-(5-*tert*-butyl-2-methylphenyl)urea



C27 H28 N4 O2; Mol wt: 440.5442

ACTION – An inhibitor of the production of inflammatory cytokines such as TNF ($IC_{50} < 10 \mu M$ in lipopolysaccharide-stimulated THP cells) and IL-1, with potential for the treatment of inflammatory and autoimmune diseases, osteoporosis, Alzheimer's disease, acute and chronic pain, atherosclerosis, stroke, myocardial infarction, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses, hemodialysis and enterocolitis. Other exemplified compounds from this series of urea derivatives include the following:



Compound	R1	R2	R3	Formula
305682	4-morpholinyl-CH2CH2	4-morpholinyl	H	C ₃₁ H ₄₀ N ₄ O ₄
305683	4-morpholinyl-CH2CH2	4-morpholinyl-CH2CH2NH	Br	C ₃₃ H ₄₄ BrN ₅ O ₄
305685	4-Pyr	Me	H	C ₂₇ H ₂₇ N ₃ O ₂
305686	3-Pyr	Me	H	C ₂₇ H ₂₇ N ₃ O ₂
305687	2-(PhOCH2)-4-morpholinyl-CH2CH2	OMe	H	C ₃₅ H ₄₁ N ₃ O ₅
305689	4-morpholinyl-CH2CH2	Me	H	C ₂₈ H ₃₅ N ₃ O ₃

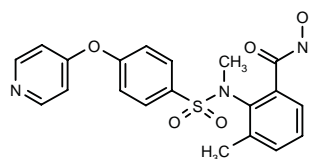
SOURCE – Boehringer Ingelheim.

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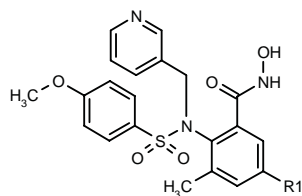
306963

3-Methyl-2-[*N*-methyl-*N*-[4-(pyridin-4-yloxy)phenyl-sulfonyl]amino]benzohydroxamic acid



C20 H19 N3 O5 S; Mol wt: 413.4521

ACTION – Potent matrix metalloproteinase (MMP) inhibitor selective for gelatinase B (MMP-9; IC₅₀ = 7 nM) and collagenase 3 (MMP-13; IC₅₀ = 4 nM) over interstitial collagenase (MMP-1; IC₅₀ = 3245 nM). Compound was shown to inhibit cartilage degradation both *in vitro* and *in vivo* in a rat sponge-wrapped cartilage model, where the dose of 50 mg/kg p.o. b.i.d. produced 35% inhibition of collagen degradation. Potentially useful for the treatment of arthritis. Other anthranilate hydroxamic acids are:



Compound	R1	Formula
306964	Ph	C ₂₇ H ₂₅ N ₃ O ₅ S
306965	2-Naph	C ₃₁ H ₂₇ N ₃ O ₅ S

SOURCE – American Home Products.

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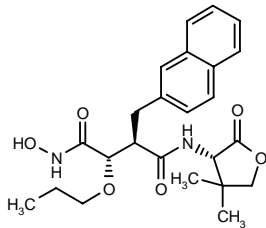
2. Levin, J.I. et al. (American Cyanamid Co.) *The preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors*. WO 9816503.

3. Levin, J.I. et al. *The discovery of anthranilic acid-based MMP inhibitors. Part 2: SAR of the 5-position P11 groups*. Bioorg Med Chem Lett 2001, 11(16): 2189.

307111

*N*¹-[4,4-Dimethyl-2-oxotetrahydrofuran-3(*S*)-yl]-*N*⁴-hydroxy-2(*R*)-(naphthalen-2-ylmethyl)-3(*S*)-propoxysuccinamide

3(*R*)-[*N*-[4,4-Dimethyl-2-oxotetrahydrofuran-3(*S*)-yl]carbamoyl]-4-(2-naphthyl)-2(*S*)-propoxybutyrohydroxamic acid



C24 H30 N2 O6; Mol wt: 442.5090

ACTION – A representative compound from a series of hydroxamic acid derivatives that inhibits the formation of human soluble CD23 (sCD23) and is indicated for the treatment of disorders related to an overproduction of sCD23, preferably allergy, inflammation and autoimmune diseases. It is reported to be a potent and selective inhibitor of CD23 and TNF release, while exhibiting reduced collagenase-inhibitory activity. Following oral administration, it also exhibited advantageous absorption properties.

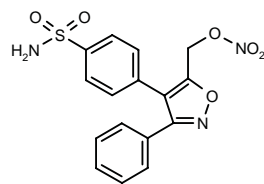
SOURCE – GlaxoSmithKline.

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307614

4-[5-(Nitrooxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide



C16 H13 N3 O6 S; Mol wt: 375.3597

ACTION – A representative compound from a series of nitrosated and nitrosylated cyclooxygenase type 2 (COX-2) inhibitors, reported to possess potent analgesic and antiinflammatory properties and improved gastrointestinal properties compared to the parent COX-2 inhibitors; they are also reported to exhibit potential for facilitating wound healing and for the treatment or prevention of renal toxicity. *In vitro*, compound was shown to inhibit ovine and human COX-2 with slightly improved selectivity compared to the parent non-nitrosated compound (ovine COX: IC₅₀ = 1.2 μM against COX-2 and no inhibition of COX-1 up to 300 μM, vs. IC₅₀ = 24 μM against COX-2 and no inhibition of COX-1 up to 300 μM; human COX: 100% inhibition of COX-2 at 10 μM vs. 65% inhibition at 10 μM). In addition, it was shown to relax phenylephrine-precontracted rat aortic smooth muscle tissue at concentrations in the range 1-100 μM, unlike the parent compound. *In vivo*, it was shown to dose-dependently inhibit carrageenan-induced paw edema following intragastric administration of 3.8 and 7.5 μmol/kg, being equipotent to the parent compound.

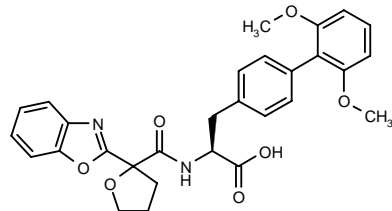
SOURCE – NitroMed.

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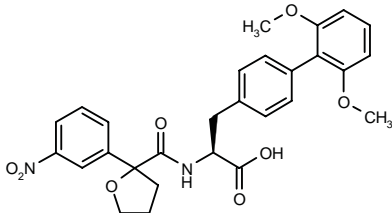
307674

N-[2-(2-Benzoxazolyl)tetrahydrofuran-2-ylcarbonyl]-4-(2,6-dimethoxyphenyl)-*L*-phenylalanine



C29 H28 N2 O7; Mol wt: 516.5472

ACTION – VLA-4 ($\alpha_4\beta_1$ integrin) antagonist shown to inhibit $\alpha_4\beta_1$ -dependent binding to VCAM–Ig fusion protein (IC_{50} = 0.42 nM) with 897-fold selectivity over $\alpha_4\beta_7$ integrin (IC_{50} = 376.9 nM). Compound exhibited favorable pharmacokinetics in rats, with low plasma clearance and high oral bioavailability. Potentially useful for the treatment of inflammatory disorders including asthma, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease. Another related compound is:



307675: C28 H28 N2 O8

SOURCE – Merck & Co.

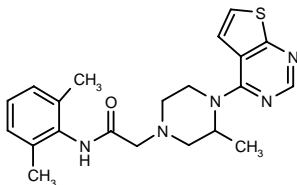
REFERENCES

1. Hagmann, W.K. et al. (Merck & Co., Inc.) *Heterocycle amides as cell adhesion inhibitors*. WO 0112183.

2. Doherty, G.A. et al. *Synthesis and structure-activity relationship of substituted tetrahydrofuroyl-1-phenylalanine derivatives as potent and selective VLA-4 antagonists*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 133.

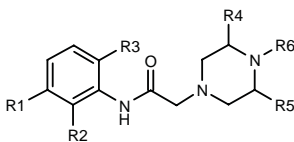
307702

(±)-N-(2,6-Dimethylphenyl)-2-[3-methyl-4-(thieno[2,3-*d*]-pyrimidin-4-yl)piperazin-1-yl]acetamide

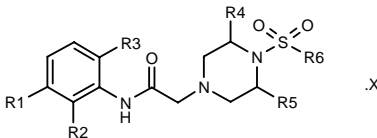


C21 H25 N5 O S; Mol wt: 395.5285

ACTION – P2X₇ receptor antagonist expected to be useful for the treatment of inflammatory, immune and cardiovascular diseases, particularly arthritis and chronic obstructive pulmonary disease. Other specifically claimed compounds from this series of piperidine and piperazine derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Isomer	Formula
307704	H	Cl	H	Me	Me	4-NH2-5-CN-2-pyrimidinyl	cis	C ₁₉ H ₂₂ ClN ₇ O
307705	1-Piz-CH2	H	Me	-(CH2)2-		thieno[2,3- <i>d</i>]-pyrimidin-4-yl		C ₂₆ H ₃₃ N ₇ OS



Compound	R1	R2	R3	R4	R5	R6	Isomer	X	Formula
307706	H	Me	H	-(CH2)2-		2-Cl-Ph			C ₂₁ H ₂₄ ClN ₃ O ₃ S
307708	F	Me	H	Me	Me	3-CN-Ph	cis		C ₂₂ H ₂₅ FN ₄ O ₃ S
307709	H	Me	Me	Me	Me	2-CN-Ph	cis	HCl	C ₂₃ H ₂₈ N ₄ O ₃ S.HCl
307710	OMe	Me	H	Me	Me	3-CN-Ph	cis		C ₂₃ H ₂₈ N ₄ O ₄ S
307711	-N=CHCH=CH-	H	H	Me		2-Pyr	3R		C ₂₁ H ₂₃ N ₅ O ₃ S

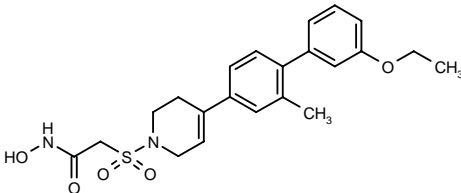
SOURCE – AstraZeneca.

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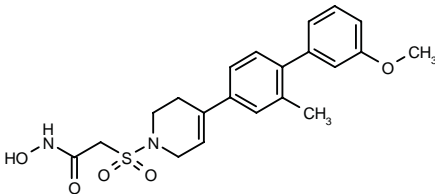
307745

2-[4-(3'-Ethoxy-2-methylbiphenyl-4-yl)-1,2,3,6-tetrahydropyridin-1-ylsulfonyl]-N-hydroxyacetamide



C22 H26 N2 O5 S; Mol wt: 430.5224

ACTION – Matrix metalloproteinase (MMP) inhibitor active against MMP-3 (stromelysin 1; IC_{50} = 4 nM), with 250-fold selectivity over MMP-2 (gelatinase A) and > 3,000-fold selectivity over MMP-1 (interstitial collagenase), MMP-9 (gelatinase B) and MMP-14 (MT-1 MMP). Potentially useful as an antiarthritic agent. Another related compound is:



307746: C21 H24 N2 O5 S

SOURCE – Pfizer.

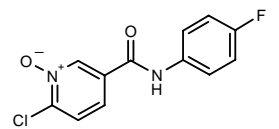
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1. Dack, K.N. and Whitlock, G.A. (Pfizer Ltd.;Pfizer Inc.) *Hydroxamic acid derivs. as matrix metalloprotease (MMP) inhibitors*. EP 1036062, WO 9929667.

2. Dack, K.N. et al. *Design and synthesis of a novel series of matrix metalloproteinase inhibitors with high selectivity for MMP-3*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 260.

307824

6-Chloro-*N*-(4-fluorophenyl)pyridine-3-carboxamide 1-oxide



C12 H8 Cl F N2 O2; Mol wt: 266.6582

ACTION – Chemokine CXCR2 antagonist, a nicotinamide *N*-oxide proven to inhibit growth-related oncogene GRO α -induced neutrophil chemotaxis (IC₅₀ = 1.1 μ M) and IL-8 binding (IC₅₀ = 1.0 μ M). Compound did not inhibit fMLP-induced neutrophil chemotaxis and exhibited low affinity for CXCR1 and CXCR2 receptors, and little or no activity at nonchemokine G-protein-coupled receptors including calcitonin, CCK_B, endothelin ET_B, somatostatin and neuropeptide Y₁ receptors. Moreover, compound inhibited IL-8-induced human neutrophil chemotaxis (IC₅₀ = 1.3-2.3 μ M), was well tolerated in mice at a dose of 100 mg/kg p.o. and was relatively stable in rat liver microsomes. Potentially useful for the treatment of inflammatory, autoimmune and allergic disorders.

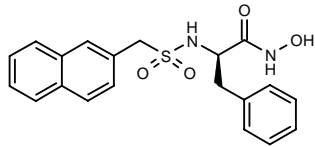
SOURCE – Celltech Group.

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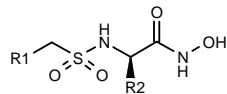
307934

*N*²-(Naphthalen-2-ylmethylsulfonyl)-*N*¹-hydroxy-D-phenylalaninamide



C20 H20 N2 O4 S; Mol wt: 384.4540

ACTION – An inhibitor of the formation of soluble human CD23 and the processing of TNF with potential in the treatment of autoimmune, inflammatory and allergic diseases. The compound inhibited the production of sCD23 in membranes of the human Epstein-Barr virus-transformed B-cell line RPMI 8866 (IC₅₀ < 1 μ M). Other exemplified sulfonamide-containing hydroxamic acids are:



Compound	R1	R2	Formula
307935	2-Naph	t-BuCH2	C ₁₈ H ₂₄ N ₂ O ₄ S
307936	2-Naph	cyclohexyl-CH2	C ₂₀ H ₂₆ N ₂ O ₄ S
307937	2-Naph	4-OH-Ph	C ₁₉ H ₁₈ N ₂ O ₅ S
307938	2-Naph	3-benzo-thienyl-CH2	C ₂₂ H ₂₀ N ₂ O ₄ S ₂

Compound	R1	R2	Formula
307939	2-Naph	(S)-i-PrCH(OH)	C ₁₇ H ₂₂ N ₂ O ₅ S
307940	5-benzothienyl	Ph	C ₁₇ H ₁₆ N ₂ O ₄ S ₂
307941	(R)-1,2,3,4-tetrahydro-2-Naph	Ph	C ₁₉ H ₂₂ N ₂ O ₄ S
307942	5-benzothienyl	3-indolyl-CH2	C ₂₆ H ₁₉ N ₃ O ₄ S ₂
307943	5-benzothienyl	4-OH-Ph	C ₁₇ H ₁₆ N ₂ O ₅ S ₂
307944	5-benzothienyl	CH2CH2Ph	C ₁₉ H ₂₀ N ₂ O ₄ S ₂
307945	5-benzothienyl	t-BuCH2	C ₁₆ H ₂₂ N ₂ O ₄ S ₂
307946	5-benzothienyl	t-Bu	C ₁₅ H ₂₀ N ₂ O ₄ S ₂
307947	5-benzothienyl	4-i-Pr-Ph	C ₂₀ H ₂₂ N ₂ O ₄ S ₂
307948	5-benzothienyl	CH2NHSO2-CH2Ph	C ₁₉ H ₂₁ N ₃ O ₆ S ₃

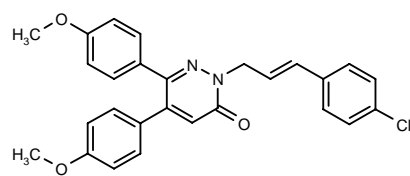
SOURCE – GlaxoSmithKline.

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308002

2-[3-(4-Chlorophenyl)-2-propenyl]-5,6-bis(4-methoxyphenyl)pyridazin-3(2*H*)-one



C27 H23 Cl N2 O3; Mol wt: 458.9427

ACTION – Potent IL-1 β production inhibitor (IC₅₀ = 0.10 μ M in HL-60 cells stimulated with lipopolysaccharide) that was orally absorbed in rats in an olive oil solution and exhibited a moderate half-life (4.9 h) and substantial plasma concentrations (C_{max} = 316.3 ng/ml). No adverse effects were seen in mice at a dose of 30 mg/kg i.p. Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Kowa.

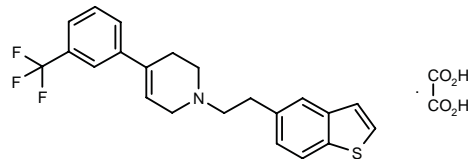
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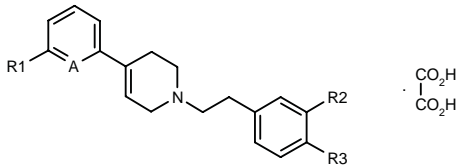
308032

1-[2-(1-Benzothien-5-yl)ethyl]-4-[3-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyridine oxalate



C22 H20 F3 N S . C2 H2 O4; Mol wt: 477.5008

ACTION – TNF- α inhibitor expected to be useful for the treatment of immune and inflammatory disorders including atherosclerosis, asthma, arthritis and fibrosis, among others. Other exemplified tetrahydropyridines are:



Compound	R1	R2,R3	A	Formula
308033	CF3	-CH=CHO-	CH	C ₂₂ H ₂₀ F ₃ NO.C ₂ H ₂ O ₄
308034	CF3	-OCH=CH-	CH	C ₂₂ H ₂₀ F ₃ NO.C ₂ H ₂ O ₄
308035	CF3	-C(Me)=C(Me)O-	CH	C ₂₄ H ₂₄ F ₃ NO.C ₂ H ₂ O ₄
308036	CF3	-CH=C(Me)O-	CH	C ₂₃ H ₂₂ F ₃ NO.C ₂ H ₂ O ₄
308037	CF3	-C(Me)=CHO-	CH	C ₂₃ H ₂₂ F ₃ NO.C ₂ H ₂ O ₄
308038	CF3	-SCH=CH-	CH	C ₂₂ H ₂₀ F ₃ NS.C ₂ H ₂ O ₄
308039	CF3	-OC(Me)=C(Me)-	CH	C ₂₄ H ₂₄ F ₃ NO.C ₂ H ₂ O ₄
308040	CF3	-SC(Me)=C(Me)-	CH	C ₂₄ H ₂₄ F ₃ NS.C ₂ H ₂ O ₄
308041	F	-C(Me)=C(Me)O-	CH	C ₂₃ H ₂₄ FNO.C ₂ H ₂ O ₄
308042	Cl	-OC(Me)=C(Me)-	N	C ₂₂ H ₂₃ ClN ₂ O.C ₂ H ₂ O ₄

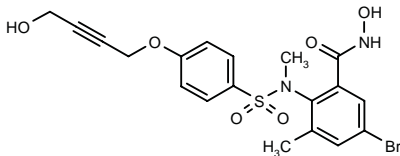
SOURCE – Sanofi-Synthélabo.

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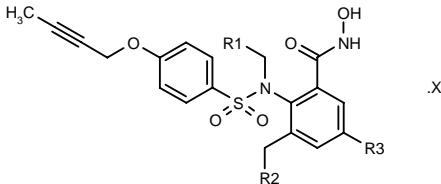
308066

5-Bromo-2-[N-[4-(4-hydroxy-2-butynyloxy)phenylsulfonyl]-N-methylamino]-3-methylbenzohydroxamic acid



C19 H19 Br N2 O6 S; Mol wt: 483.3371

ACTION – TNF- α -converting enzyme (TACE) and matrix metalloproteinase (MMP) inhibitor proven to inhibit MMP-1 (fibroblast collagenase), MMP-9 (gelatinase B), MMP-13 (collagenase 3) and TACE with IC₅₀ values of 3203, 477, 83 and 6.8 nM, respectively. In addition, this compound was shown to inhibit lipopolysaccharide-stimulated TNF- α production in human monocytic THP-1 cells (88% inhibition at 3 μ M). Potentially useful for the treatment of rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory diseases of the CNS, inflammatory bowel disease and HIV infection. Other exemplified alkynyl-containing hydroxamic acids are:



Compound	R1	R2	R3	X	Formula
308068	H	H	I		C ₁₉ H ₁₉ IN ₂ O ₅ S
308069	4-Me-1-Piz	H	Br		C ₂₄ H ₂₉ BrN ₄ O ₅ S
308070	H	4-Me-1-Piz	Ph	2HCl	C ₃₀ H ₃₄ N ₄ O ₅ S.2HCl

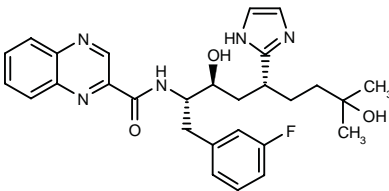
SOURCE – American Home Products.

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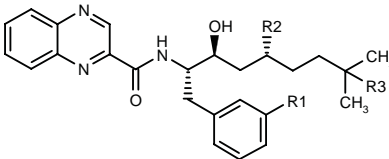
308122

N-[1(S)-(3-Fluorobenzyl)-2(S),7-dihydroxy-4(R)-(1H-imidazol-2-yl)-7-methyloctyl]quinoxaline-2-carboxamide



C28 H32 F N5 O3; Mol wt: 505.5908

ACTION – A chemokine CCR1 receptor antagonist with potential in the treatment of autoimmune and inflammatory diseases, allergy, infection associated with inflammation, viral chronic bronchitis, transplant rejection, atherosclerosis, restenosis, HIV infection and granulomatous diseases. Other specifically claimed heterocyclic amide derivatives are:



Compound	R1	R2	R3	Formula
308125	F	2-imidazolyl	F	C ₂₈ H ₃₁ F ₂ N ₅ O ₂
308126	F	SO ₂ NH ₂	OH	C ₂₅ H ₃₁ FN ₄ O ₅ S
308127	F	SO ₂ NH ₂	F	C ₂₅ H ₃₀ F ₂ N ₄ O ₄ S
308129	F	SO ₂ NHMe	OH	C ₂₆ H ₃₃ FN ₄ O ₅ S
308131	H	SO ₂ NHMe	F	C ₂₆ H ₃₃ FN ₄ O ₄ S
308133	H	4-Cl-2-imidazolyl	OH	C ₂₈ H ₃₂ ClN ₅ O ₃
308135	H	4-Cl-2-imidazolyl	F	C ₂₈ H ₃₁ ClFN ₅ O ₂
308137	H	4-F-2-imidazolyl	F	C ₂₈ H ₃₁ F ₂ N ₅ O ₂

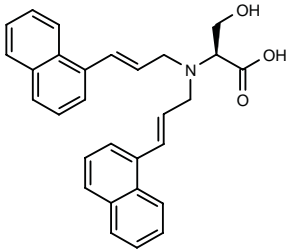
SOURCE – Pfizer.

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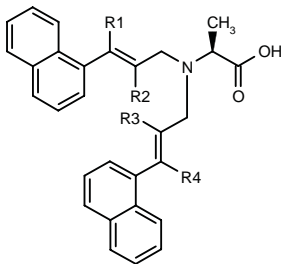
308170

N,N-Bis[3-(1-naphthyl)-2-propenyl]-L-serine



C29 H27 N O3; Mol wt: 437.5363

ACTION – Neutral sphingomyelinase inhibitor with an IC₅₀ of 1.8 μM in a sphingomyelinase-containing lysate preparation. Potentially useful for the treatment of rheumatoid arthritis, gastrointestinal inflammatory disease, asthma, psoriasis and B- and T-cell lymphomas. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
308171	H	H	H	H	C ₂₉ H ₂₇ NO ₂
308173	bond		bond		C ₂₉ H ₂₃ NO ₂

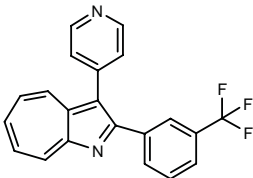
SOURCE – Ortho-McNeil.

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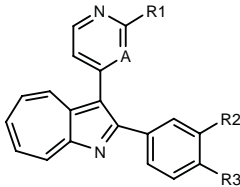
308331

3-(4-Pyridyl)-2-[3-(trifluoromethyl)phenyl]cyclohepta[*b*]pyrrole



C21 H13 F3 N2; Mol wt: 350.3417

ACTION – Antiinflammatory agent, an inhibitor of p38 MAP kinase (IC₅₀ = 1470 nM) and TNF-α production. It inhibited lipopolysaccharide-induced TNF-α secretion in human monocytic leukemia THP-1 cells with an IC₅₀ of 160 nM. Other specifically claimed cyclohepta[*b*]pyrrole derivatives are:



Compound	R1	R2	R3	A	Formula
308332	H	H	F	CH	C ₂₀ H ₁₃ FN ₂
308333	F	H	F	CH	C ₂₀ H ₁₂ F ₂ N ₂
308334	SMe	H	F	N	C ₂₀ H ₁₄ FN ₃ S
308335	NHMe	H	F	N	C ₂₀ H ₁₅ FN ₄
308336	NHMe	CF3	H	N	C ₂₁ H ₁₅ F ₃ N ₄
308337	F	CF3	H	CH	C ₂₁ H ₁₂ F ₄ N ₂
308338	H	H	OMe	CH	C ₂₁ H ₁₆ N ₂ O
308339	H	H	Cl	CH	C ₂₀ H ₁₃ ClN ₂
308340	H	Cl	H	CH	C ₂₀ H ₁₃ ClN ₂
308342	F	Cl	H	CH	C ₂₀ H ₁₂ ClFN ₂
308343	H	H	Me	CH	C ₂₁ H ₁₆ N ₂

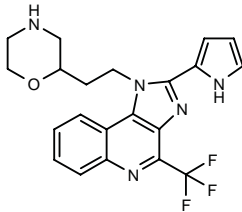
SOURCE – Abbott.

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308606

1-[2-(2-Morpholinyl)ethyl]-2-(1 *H*-pyrrol-2-yl)-4-(trifluoromethyl)-1 *H*-imidazo[4,5-*c*]quinoline



C21 H20 F3 N5 O; Mol wt: 415.4170

ACTION – Inhibitor of cytokine production, as demonstrated against lipopolysaccharide-stimulated TNF-α and IL-1β production in human peripheral blood mononuclear cells (96 and 81% inhibition, respectively, at 0.01 μM). Potentially useful for the treatment of chronic inflammatory diseases, allergic rhinitis, atopic dermatitis, asthma, septic shock, autoimmune diseases, diabetes, cancer- and AIDS-related cachexia, etc.

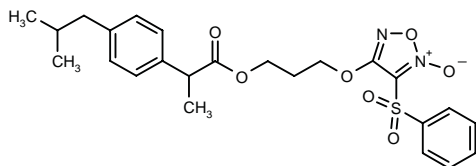
SOURCE – Hokuriku.

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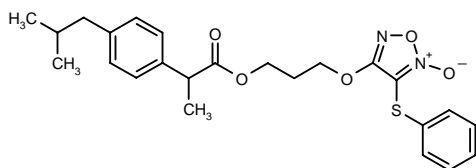
309101

2-(4-Isobutylphenyl)propionic acid 3-[5-oxido-4-(phenylsulfonyl)-1,2,5-oxadiazol-3-yloxy]propyl ester



C₂₄ H₂₈ N₂ O₇ S; Mol wt: 488.5582

ACTION – Nonsteroidal antiinflammatory agent consisting of ibuprofen linked to a nitric oxide (NO)-donating furoxan moiety. In the rat carrageenan-induced paw edema model, compound exhibited comparable antiinflammatory activity to ibuprofen, but unlike the latter, it was not associated with acute gastric lesions. Moreover, compound inhibited arachidonic acid-induced aggregation of human platelet-rich plasma with a pIC₅₀ of 6.2, being at least as potent as ibuprofen. Another related compound is:



309102: C₂₄ H₂₈ N₂ O₅ S

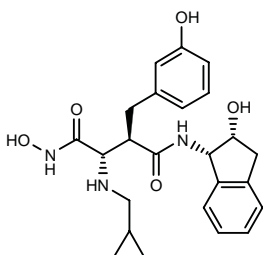
SOURCES – Istituto di Ricerche Farmacologiche Mario Negri, Milano (IT); Università degli Studi di Parma, Parma (IT); Università degli Studi di Torino (IT).

REFERENCES

1. Lolli, M.L. et al. *A new class of ibuprofen derivatives with reduced gastrotoxicity*. J Med Chem 2001, 44(21): 3463.

309116

2(S)-(Cyclopropylmethylamino)-N¹-hydroxy-3(R)-(3-hydroxybenzyl)-N⁴-[2(R)-hydroxy-2,3-dihydro-1H-inden-1(S)-yl]butanediamide



C₂₄ H₂₉ N₃ O₅; Mol wt: 439.5091

ACTION – Potent and selective aggrecanase inhibitor with an IC₅₀ value of 12 nM and respective K_i values of 171, 33,160, 6300 and 4468 nM against MMP-8 (neutrophil collagenase), MMP-1 (interstitial collagenase), MMP-2 (gelatinase A) and MMP-9 (gelatinase B). Compound showed a good pharmacokinetic profile in dogs, with an oral bioavailability of 43%, a terminal half-life of 6 h and low systemic clearance (0.5 l/h/kg). Potentially useful as a tool for further elucidating the biological function of aggrecanase, as well as for the treatment of degenerative joint diseases.

SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

REFERENCES

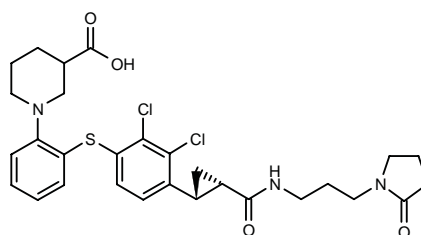
1. Yao, W. and DeCicco, C.P. (DuPont Pharmaceuticals Co.) *Novel inhibitors of aggrecanase and matrix metalloproteinases for the treatment of arthritis*. WO 9909000.

2. Yao, W. et al. *Design and synthesis of a series of (2R)-N4-hydroxy-2-(3-hydroxybenzyl)-N1-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]butanediamide derivatives as potent, selective, and orally bioavailable aggrecanase inhibitors*. J Med Chem 2001, 44(21): 3347.

A-324920

307553

1-[2-[2,3-Dichloro-4-[*trans*-2-[N-[3-(2-oxopyrrolidin-1-yl)-propyl]carbamoyl]cyclopropyl]phenylsulfanyl]phenyl]piperidine-3-carboxylic acid



C₂₉ H₃₃ Cl₂ N₃ O₄ S; Mol wt: 590.5687

ACTION – Cell adhesion inhibitor, an antagonist of the LFA-1/ICAM-1 interaction (IC₅₀ = 5 nM in the absence of serum; IC₅₀ = 27 nM in the presence of serum) proven to be active in the JY-8 lymphoblastoid cell/ICAM-1 adhesion assay (IC₇₀ = 9 nM in the absence of serum; IC₇₀ = 200 nM in the presence of serum). Potentially useful for the treatment of inflammatory diseases, autoimmune diseases, tumor metastasis, transplant rejection and reperfusion injury.

SOURCE – Abbott.

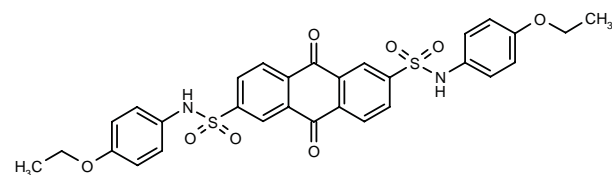
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1. Link, J.T. et al. *Discovery and SAR of diarylsulfide cyclopropylamide LFA-1/ICAM-1 interaction antagonists*. Bioorg Med Chem Lett 2001, 11(8): 973.

GR-377

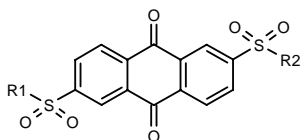
309135

N,N'-Bis(4-ethoxyphenyl)-9,10-dioxo-9,10-dihydroanthracene-2,6-disulfonamide



C₃₀ H₂₆ N₂ O₈ S₂; Mol wt: 606.6734

ACTION – Chondroprotective agent, an anthraquinone with uncompetitive micromolar inhibitory activity against human cathepsin A and B; compound was inactive against cyclooxygenase 1 (COX-1), but inhibited COX-2, nitric oxide synthase (NOS) and IL-1 β -induced proteoglycan release from bovine articular cartilage at micromolar concentrations. Potentially useful for the treatment of osteoarthritis. Other related compounds are:



Compound	R1=R2	Formula
GR-373 [309132]	OH	C ₁₄ H ₈ O ₈ S ₂
GR-375 [309133]	NHEt	C ₁₈ H ₁₈ N ₂ O ₆ S ₂

SOURCE – Gentili.

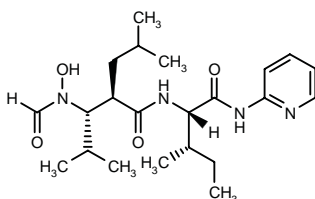
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- Benetti, D. et al. (Istituto Gentili SpA) *Mono- and disulfo-substd. anthraquinones and their use for the treatment of bone matrix disorders*. WO 9700675.
- Mian, M. et al. *In vitro chondroprotective activity of a novel class of anthraquinones*. Osteoarthritis Cartilage 2001, 9(Suppl. B): Abst PA10.

GW-3333*

272734

N α -[3(*S*)-(N-Hydroxyformamido)-2(*R*)-isobutyl-4-methylpentanoyl]-*N*¹-(2-pyridyl)-L-isoleucylamide



C22 H36 N4 O4; Mol wt: 420.5504

ACTION – Dual inhibitor of TNF- α -converting enzyme (TACE; IC₅₀ = 40 nM) and matrix metalloproteinases (MMPs) including collagenase 1 (MMP-1), gelatinase A (MMP-2), stromelysin 1 (MMP-3), neutrophil collagenase (MMP-8), gelatinase B (MMP-9) and collagenase 3 (MMP-13), with IC₅₀s ranging from 4 to 20 nM. Compound completely inhibited lipopolysaccharide (LPS)-induced TNF release from human Mono Mac-6 cells (IC₅₀ = 0.17 μ M) and peripheral blood mononuclear cells (PBMCs; IC₅₀ = 0.97 μ M). In rats, a dose of 80 mg/kg p.o. completely inhibited LPS-stimulated TNF production for up to 12 h and prevented TNF accumulation in the pleural cavity in a zymosan-induced pleurisy model. Furthermore, compound was found to inhibit swelling and inflammation in two models of arthritis in rats; in a model of local arthritis induced by peptidoglycan polysaccharide polymers, a dose of 80 mg/kg p.o. b.i.d. significantly reduced swelling, and in a 21-day adjuvant arthritis model, doses of 50 and 150 mg/kg b.i.d. on days 7-21 significantly decreased ankle swelling and bone and cartilage destruction, and induced significant radiological improvement. Potentially useful for the treatment of arthritis.

SOURCE – GlaxoSmithKline.

REFERENCES

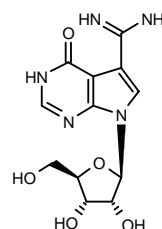
- Andrews, R.C. et al. (Glaxo Wellcome plc) *Reverse hydroxamate derivs. as metalloprotease inhibitors*. EP 1019386, JP 2001513767, WO 9838179.
- Conway, J.G. et al. *Inhibition of tumor necrosis factor- α (TNF- α) production and arthritis in the rat by GW3333, a dual inhibitor of TNF- α -converting enzyme and matrix metalloproteinases*. J Pharmacol Exp Ther 2001, 298(3): 900.

*Identified compound **272734** Drug Data Rep 1999, 021(04): 0349.

ICN-10776*

291177

4-Oxo-7-(β -D-ribofuranosyl)-4,7-dihydro-3*H*-pyrrolo-[2,3-*d*]pyrimidine-5-carboxamide



C12 H15 N5 O5; Mol wt: 309.2805

ACTION – Immunomodulating agent, a nucleoside analogue with cytokine-modulating activity both *in vitro* and *in vivo*. In particular, compound inhibited PMA/ionomycin-induced type 1 cytokine (interferon gamma, IL-2 and TNF- α) production and enhanced type 2 cytokine (IL-4 and IL-5) production in T-cells from healthy subjects, as well as inhibiting interferon gamma production and enhancing IL-4 production in cells from rheumatoid arthritis patients. In mice, compound (0.6 mg/kg i.p.) inhibited a Th1-mediated immune response such as DNFB-induced contact hypersensitivity, an effect associated with increased IL-10 and decreased interferon gamma mRNA expression. Potentially useful for the treatment of chronic inflammatory disorders such as rheumatoid arthritis.

SOURCE – ICN.

REFERENCES

- Tam, R. et al. (ICN Pharmaceuticals, Inc.) *Nucleoside analogs with carboxamidino-modified bicyclic base*. WO 0160381.
- Wang, G. et al. (ICN Pharmaceuticals, Inc.) *Pyrrolo[2,3-*d*]pyrimidine nucleoside analogs*. WO 0127114.
- Hinshaw, B.C. et al. *Pyrrolopyrimidine nucleosides. V. A study on the relative chemical reactivity of the 5-cyano group of the nucleoside antibiotic toyocamycin and desaminotoyocamycin. The synthesis of analogs of sangivamycin*. J Org Chem 1970, 35(1): 236.
- Tam, R.C. et al. *Induction of a Th2 cytokine bias by the nucleoside analogue ICN 10776 can inhibit a type 1-mediated immune response in vivo*. FASEB J 2000, 14(6): Abst 51.9.
- Wang, G. et al. *Synthesis and cytokine modulation properties of pyrrolo[2,3-*d*]-4-pyrimidinone nucleosides*. J Med Chem 2000, 43(13): 2566.

*Identified compound **291177** Drug Data Rep 2000, 022(09): 0832.

IMMUNOMODULATING AGENTS

ALLOFERON-1

307452

L-Histidyl-glycyl-L-valyl-L-seryl-glycyl-L-histidyl-glycyl-L-glutaminyl-L-histidyl-glycyl-L-valyl-L-histidyl-glycine

C52 H76 N22 O16; Mol wt: 1265.3100

ACTION – Immunomodulatory peptide isolated from the blood of bacteria-challenged larvae of the insect *Calliphora vicina*, reported to be able to stimulate antiviral, antimicrobial and antitumor immune responses. Alloferon-1 enhanced the cytotoxicity of both murine spleen lymphocytes and human peripheral blood lymphocytes against human leukemia K-562. *In vivo*, the compound reduced the mortality rate of influenza virus-infected mice following i.p. administration (0.5 mg/kg), and gave no signs of acute or chronic toxicity.

SOURCE – Entopharm.

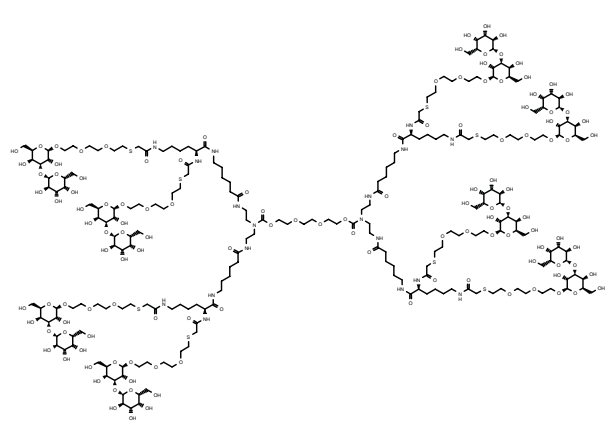
REFERENCES

1. Kim, S.I. et al. (Entopharm Co., Ltd.) *Alloferons - Immunomodulatory peptides*. EP 1114829.

LJP-920

270611

30-[3-O-(α-D-Galactopyranosyl)-β-D-galactopyranosyloxy]-14(S)-[11-[3-O-(α-D-galactopyranosyl)-β-D-galactopyranosyloxy]-6,9-dioxo-3-thiaundecanamido]-2-[28-[3-O-(α-D-galactopyranosyl)-β-D-galactopyranosyloxy]-12(S)-[11-[3-O-(α-D-galactopyranosyl)-β-D-galactopyranosyloxy]-6,9-dioxo-3-thiaundecanamido]-4,11,18-trioxo-23,26-dioxo-20-thia-3,10,17-triazaoctacosyl]-6,13,20-trioxo-25,28-dioxo-22-thia-2,5,12,19-tetraazatriacontanoic acid 3,6-dioxaoctane-1,8-diyl diester



C224 H400 N18 O126 S8; Mol wt: 5618.1520

ACTION – Agent for prevention of xenotransplant rejection, an octameric conjugate composed of Gal (α1-3) Gal coupled to a nonimmunogenic platform, proven to clear circulating α-galactose antibodies and inhibit their production by B-cells. The conjugate did not show

enzymatic degradation in mouse serum or liver microsomes for up to 48 h. Pharmacokinetic experiments in mice showed a short serum half-life (30 min), higher distribution in serum than in erythrocytes and predominantly renal excretion in unchanged form.

SOURCE – La Jolla Pharmaceutical.

REFERENCES

1. Jack, R.M. et al. (La Jolla Pharmaceutical Co.) *Conjugates comprising galactose alpha 1,3 galactosyl epitopes and methods of using same*. EP 1137652, WO 0034296.

2. Jack, R.M. et al. (La Jolla Pharmaceutical Co.) *Methods and formulations for reducing circulating antibodies*. WO 0033887.

3. Jia, L. et al. *Biostability and pharmacokinetics of LJP 920, an octameric Gal (α1-3) Gal conjugate for the inhibition of xenotransplantation rejection*. J Pharm Pharmacol 2001, 53(7): 999.

4. Jia, L. et al. *Stability and pharmacokinetics of LJP 920, an octameric Gal (α1-3) Gal conjugate for inhibition of xenotransplantation rejection*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

5. *Further positive results received from animal studies of La Jolla's xenotransplantation compound*. DailyDrugNews.com (Daily Essentials) 1999, May 5.

6. *La Jolla Pharmaceutical updates progress with lupus drug*. DailyDrugNews.com (Daily Essentials) 2000, Feb 29.

7. *La Jolla presents positive results from animal studies of xenotransplantation drug*. DailyDrugNews.com (Daily Essentials) 1999, Dec 17.

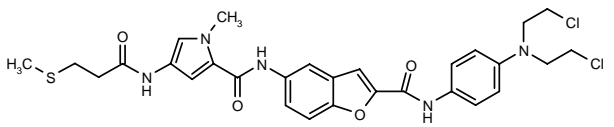
8. *La Jolla presents promising primate data on new xenotransplantation Toleragen candidate*. DailyDrugNews.com (Daily Essentials) 1998, Dec 14.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

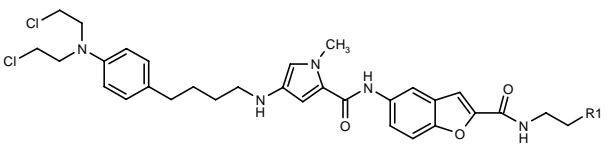
308344

N-[2-[N-[4-[N,N-Bis(2-chloroethyl)amino]phenyl]carbonyl]-1-benzofuran-5-yl]-1-methyl-4-[3-(methylsulfonyl)propionamido]-1H-pyrrole-2-carboxamide



C29 H31 Cl2 N5 O4 S; Mol wt: 616.5669

ACTION – DNA-targeted anticancer agent giving an IC₅₀ of 0.31 µg/ml against the murine B16 melanoma cell line. Other exemplified benzofuranyl-containing pyrrole-2-carboxamides include the following:



Compound	R1	Formula
308346	CH2N(Me)2	C ₃₄ H ₄₂ Cl ₂ N ₆ O ₄
308348	C(=NH)NH2	C ₃₂ H ₃₇ Cl ₂ N ₇ O ₄

IMMUNOMODULATING AGENTS

ALLOFERON-1

307452

L-Histidyl-glycyl-L-valyl-L-seryl-glycyl-L-histidyl-glycyl-L-glutaminyl-L-histidyl-glycyl-L-valyl-L-histidyl-glycine

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SOURCE – Entopharm.

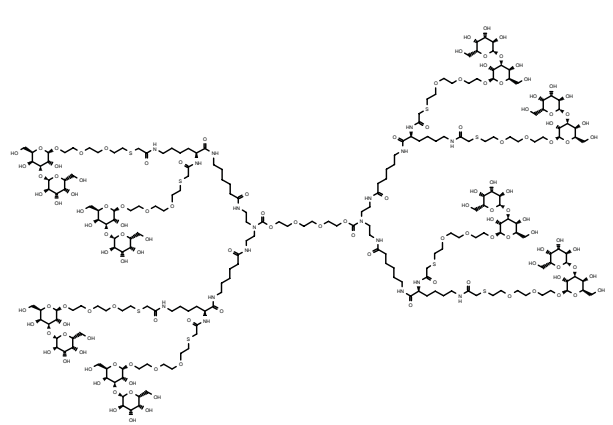
REFERENCES

1. Kim, S.I. et al. (Entopharm Co., Ltd.) *Alloferons - Immunomodulatory peptides*. EP 1114829.

LJP-920

270611

30-[3-O-(α-D-Galactopyranosyl)-β-D-galactopyranosyloxy]-14(S)-[11-[3-O-(α-D-galactopyranosyl)-β-D-galactopyranosyloxy]-6,9-dioxa-3-thiaundecanamido]-2-[28-[3-O-(α-D-galactopyranosyl)-β-D-galactopyranosyloxy]-12(S)-[11-[3-O-(α-D-galactopyranosyl)-β-D-galactopyranosyloxy]-6,9-dioxa-3-thiaundecanamido]-4,11,18-trioxo-23,26-dioxa-20-thia-3,10,17-triazaoctacosyl]-6,13,20-trioxo-25,28-dioxa-22-thia-2,5,12,19-tetraazatriacontanoic acid 3,6-dioxaoctane-1,8-diyl diester



C224 H400 N18 O126 S8; Mol wt: 5618.1520

ACTION – Agent for prevention of xenotransplant rejection, an octameric conjugate composed of Gal (α1-3) Gal coupled to a nonimmunogenic platform, proven to clear circulating α-galactose antibodies and inhibit their production by B-cells. The conjugate did not show

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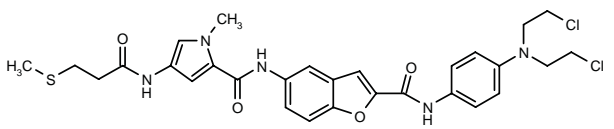
8. *La Jolla presents promising primate data on new xenotransplantation Toleragen candidate*. DailyDrugNews.com (Daily Essentials) 1998, Dec 14.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

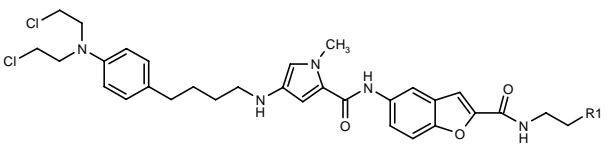
308344

N-[2-[N-[4-[N,N-Bis(2-chloroethyl)amino]phenyl]carbonyl]-1-benzofuran-5-yl]-1-methyl-4-[3-(methylsulfonyl)propionamido]-1H-pyrrole-2-carboxamide

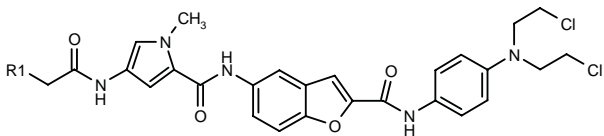


C29 H31 Cl2 N5 O4 S; Mol wt: 616.5669

ACTION – DNA-targeted anticancer agent giving an IC₅₀ of 0.31 µg/ml against the murine B16 melanoma cell line. Other exemplified benzofuranyl-containing pyrrole-2-carboxamides include the following:



Compound	R1	Formula
308346	CH2N(Me)2	C ₃₄ H ₄₂ Cl ₂ N ₆ O ₄
308348	C(=NH)NH2	C ₃₂ H ₃₇ Cl ₂ N ₇ O ₄



Compound	R1	Formula
308347	CH2S(Me)2 ⁺ I ⁻	C ₃₀ H ₃₄ Cl ₂ IN ₆ O ₄ S
308350	NHC(=NH)NH ₂	C ₂₈ H ₃₀ Cl ₂ N ₆ O ₄

SOURCE – Mitsui Chemicals.

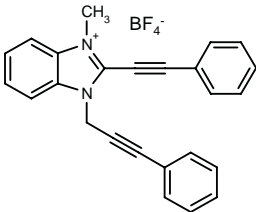
REFERENCES

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AZB-002

296332

1-Methyl-2-(2-phenylethynyl)-3-(3-phenyl-2-propynyl)-3H-benzimidazol-1-ium tetrafluoroborate



C25 H19 N2 . B F4; Mol wt: 434.2421

ACTION – DNA-cleaving antitumor agent reported to induce supercoiled and oligonucleotide DNA cleavage and thereby produce multiple DNA lesions. Compound exhibited broad-spectrum cytotoxic activity against human cancer cell lines, especially against lung carcinoma A549 cells (IC₅₀ = 0.83 μM). In mice bearing A549 xenografts, compound (3-10 mg/kg) produced dose-dependent tumor growth inhibition, but the dose of 10 mg/kg was associated with systemic toxicity.

SOURCE – University of Texas System, Austin, TX (US).

REFERENCES

1. Kerwin, S.M. and David, W. (University of Texas System) *Novel DNA-cleaving antitumor agents.* EP 1109552, US 6297284, WO 0003709, WO 0170217.

2. David, W.M. et al. *Synthesis of a heterocyclic aza-enediyne and its DNA-cleavage properties.* Bioorg Med Chem Lett 2000, 10(22): 2509.

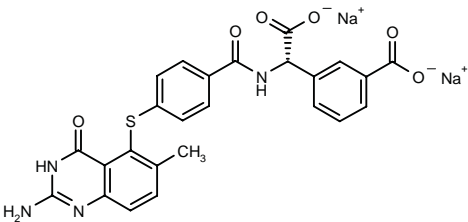
3. Kerwin, S.M. et al. *DNA cleavage chemistry of 1-methyl-2-phenylethynyl-3-(prop-2-ynyl)-3H-benzimidazolium salts.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 146.

ANTIMETABOLITES

CW-252053*

270681

2(S)-[4-(2-Amino-6-methyl-4-oxo-3,4-dihydroquinazolin-5-ylsulfanyl)benzamido]-2-(3-carboxyphenyl)acetic acid disodium salt



C25 H18 N4 Na2 O6 S; Mol wt: 548.4852

ACTION – Antineoplastic agent, a quinazoline folate-based thymidylate synthase inhibitor reported to inhibit the growth of murine and human tumor cells including murine leukemia L1210, thymidine kinase-deficient murine lymphoma LY TK^{-/-}, human leukemia CCRF-CEM and human colon adenocarcinoma HT-29 cells (IC₅₀ = 0.05-1.2 μM). In *in vivo* studies in mice bearing LY3.7.2c TK^{-/-}, compound at a dose of 60 mg/kg i.p. b.i.d. produced cure in 37.5% of animals and a 50% survival rate, and complete tumor growth inhibition was seen at a dose of 120 mg/kg i.p. b.i.d. For comparison, 5-FU at 10 mg/kg i.p. did not produce cure and only slightly increased the life span. No systemic toxicity was seen with compound at the administered doses over the entire treatment period (35 days).

SOURCE – Choongwae.

REFERENCES

1. Baek, D.-J. et al. *Synthesis of 5-substituted quinazolinone derivatives and their inhibitory activity in vitro.* Bioorg Med Chem Lett 1998, 8(23): 3287.

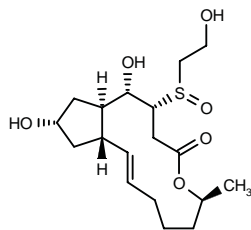
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*Identified compound **270681** Drug Data Rep 1999, 021(03): 0264.

ANTIBIOTICS AND ALKALOIDS

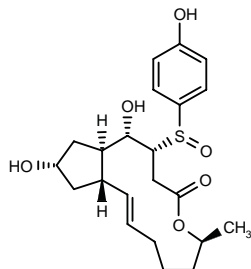
268122

(1*S*,2*R*,6*S*,10*E*,11*aS*,13*S*,14*aR*)-1,13-Dihydroxy-2-(2-hydroxyethylsulfinyl)-6-methyl-2,3,4,6,7,8,9,11*a*,12,13,14,14*a*-dodecahydro-1*H*-cyclopenta[*f*]oxacyclotridecin-4-one



C18 H30 O6 S; Mol wt: 374.4950

ACTION – Macrolide antibiotic, a brefeldin A sulfide prodrug with enhanced aqueous solubility. It showed *in vitro* antiproliferative activity against human cancer cells and *in vivo* efficacy in the rat hollow fiber assay. Another related compound is:



268121: C22 H30 O6 S

SOURCE – Purdue University, West Lafayette, IN (US).

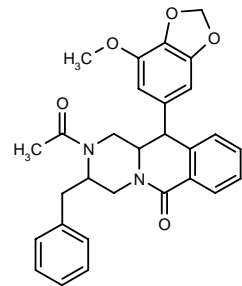
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2. Argade, A.B. et al. *Design and synthesis of brefeldin A sulfide derivatives as prodrug candidates with enhanced aqueous solubilities.* J Med Chem 1998, 41(18): 3337.
3. Fox, B.M. et al. *Design and synthesis of (+)-brefeldin A sulfide prodrugs with enhanced aqueous solubilities.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MED1 97.

PF-1185A

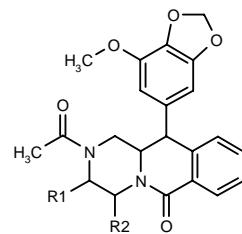
307257

2-Acetyl-3-benzyl-11-(7-methoxy-1,3-benzodioxol-5-yl)-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinolin-6-one



C29 H28 N2 O5; Mol wt: 484.5492

ACTION – Antineoplastic antibiotic obtained from the fungus *Chrysosporium* sp. PF1185 (FERM P-17603) that is potentially useful as an anticancer agent and for overcoming multidrug resistance. Other compounds from the same source are:



Compound	R1	R2	Formula
PF-1185B [307258]	COPh	H	C ₂₉ H ₂₆ N ₂ O ₆
PF-1185C [307260]	bond		C ₂₂ H ₂₀ N ₂ O ₅

SOURCE – Meiji Seika.

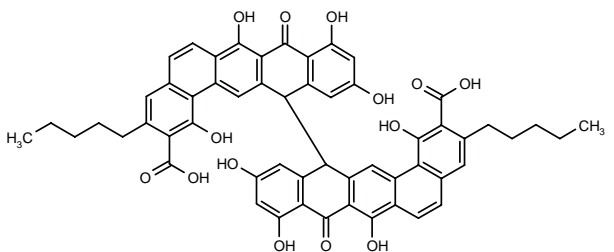
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TEL-68M

307240

1,1',7,7',9,9',11,11'-Octahydroxy-8,8'-dioxo-3,3'-dipentyl-8,8',13,13'-tetrahydro-13,13'-bibenzo[*a*]tetracene-2,2'-dicarboxylic acid



C56 H46 O14; Mol wt: 942.9654

ACTION – Antineoplastic antibiotic isolated from *Streptomyces* sp. TEL68 (FERM BP-6950). TEL-68M was particularly active against *Bacillus subtilis* (MIC < 0.04 µg/ml). When tested *in vitro* against the human epidermal cancer and renal cancer cell lines A-431 and ACHN, it gave IC₅₀ values of 3.8 and 5.3 µM, respectively.

SOURCE – Kyowa Hakko.

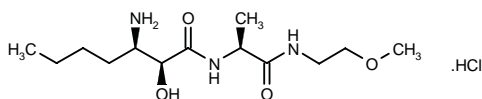
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1. Asai, A. et al. (Kyowa Hakko Kogyo Co., Ltd.) *TEL68M cpds.* JP 2001158759.

ANGIOGENESIS INHIBITORS

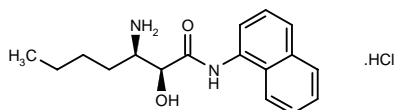
305498

N-[3(*R*)-Amino-2(*S*)-hydroxyheptanoyl]-L-alanine 2-methoxyethylamide hydrochloride



C13 H27 N3 O4 . HCl; Mol wt: 325.8342

ACTION – Nonpeptide, reversible inhibitor of type 2 methionine aminopeptidase (MetAP2), potentially useful for the treatment of conditions mediated by angiogenesis such as cancer, hemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity. Another exemplified compound is:



305499: C17 H22 N2 O2 . HCl

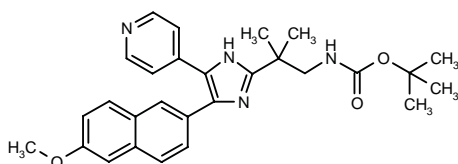
SOURCE – GlaxoSmithKline.

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305584

N-[2-[4-(6-Methoxynaphthalen-2-yl)-5-(4-pyridyl)-1*H*-imidazol-2-yl]-2-methylpropyl]carbamic acid *tert*-butyl ester



C28 H32 N4 O3; Mol wt: 472.5858

ACTION – An inhibitor of Tie2 receptor kinase activity (IC₅₀ < 1 µM) with potential for the treatment or prevention of proliferative disorders and chronic inflammatory disorders caused by excessive or inappropriate angiogenesis such as cancer, metastasis, arthritis, psoriasis, atherosclerosis, diabetic retinopathy and macular degeneration. A representative compound from a series of substituted imidazole derivatives.

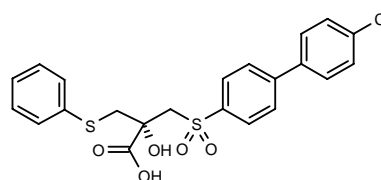
SOURCE – GlaxoSmithKline.

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305678

3-(4'-Chlorobiphenyl-4-ylsulfonyl)-2(*R*)-hydroxy-2-(phenylsulfanylmethyl)propionic acid



C22 H19 Cl O5 S2; Mol wt: 462.9721

ACTION – An inhibitor of matrix metalloproteinases (MMPs) with K_i values of 9 and 7180 nM, respectively, against human gelatinase A (MMP-2) and human fibroblast collagenase (MMP-1), also shown to inhibit collagenase 3 (MMP-13; K_i = 40.5 nM) and membrane type I MMP (MMP-14; K_i = 192 nM). *In vivo* it displayed antitumor activity when administered to nude mice bearing human prostate carcinoma DU 145 xenografts (44-56% inhibition of tumor growth at 100-200 mg/kg/day p.o.) or human colon carcinoma HCT 116 xenografts (60% inhibition of tumor growth at 200 mg/kg/day p.o.), as well as in an experimental model of metastasis (45-61% reduction of number of human melanoma A 375/m metastases at 100-200 mg/kg/day p.o.). In pharmacokinetic studies in rats and monkeys, it exhibited an oral bioavailability of 27 and 60%, respectively, when administered as the sodium salt. No signs of toxicity were observed following single doses of 2000 mg/kg p.o. to rats and monkeys, nor after administration of 300 mg/kg/day p.o. x 15 days to rats.

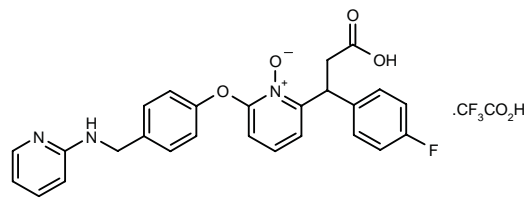
SOURCE – Pharmacia.

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1. Bissolino, P. et al. (Pharmacia & Upjohn SpA) *(R)-3-(4-Chlorobiphenyl-sulfonyl)-2-hydroxy-2-(phenylthio)methylpropionic acid and its use matrix metalloproteinase.* WO 0138301.

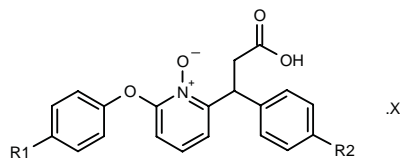
307118

3-(4-Fluorophenyl)-3-[1-oxido-6-[4-(pyridin-2-ylamino-methyl)phenoxy]pyridin-2-yl]propionic acid trifluoroacetate

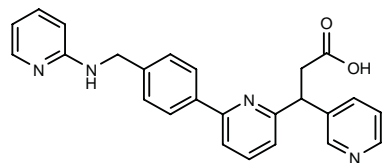


C26 H22 F N3 O4 . C2 H F3 O2; Mol wt: 573.4967

ACTION – Selective $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin inhibitor expected to be useful in the treatment of inflammatory disorders and angiogenesis-related diseases, particularly for the treatment of tumors, arthritis, osteoporosis, psoriasis, vascular restenosis, atherosclerosis, etc. Other specifically claimed propionic acid derivatives are:



Compound	R1	R2	X	Formula
307120	2-benzimidazolyl-NHCH2	F	CF3CO2H	C ₂₈ H ₂₃ FN ₄ O ₄ ·C ₂ HF ₃ O ₂
307121	2-benzimidazolyl-NHCH2	CO2H		C ₂₉ H ₂₄ N ₄ O ₆
307122	6-NH2-2-Pyr	CO2H	CF3CO2H	C ₂₆ H ₂₁ N ₅ O ₆ ·C ₂ HF ₃ O ₂
307123	2-Pyr-NHCH2	CO2H	CF3CO2H	C ₂₇ H ₂₃ N ₅ O ₆ ·C ₂ HF ₃ O ₂



307119: C25 H22 N4 O2

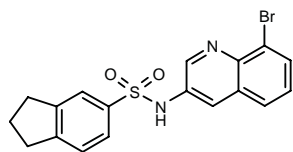
SOURCE – Celltech Group.

REFERENCES

1. Alexander, R.P. et al. (Celltech Chiroscience Ltd.) *Propanoic acid derivs. as integrin inhibitors*. WO 0144194.

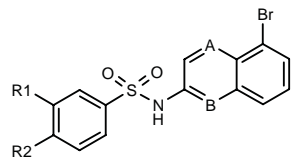
307409

N-(8-Bromoquinolin-3-yl)indane-5-sulfonamide



C18 H15 Br N2 O2 S; Mol wt: 403.2985

ACTION – Neovascularization inhibitor shown to inhibit collagen-induced neovascularization in rat thoracic aorta with an IC₅₀ of 0.04 µg/ml. Potentially useful for the treatment of cancer, metastasis, diabetic retinopathy, rheumatoid arthritis and hemangioma. Other exemplified heterocyclic compounds with sulfonamide or sulfonylurea groups are:



Compound	R1	R2	A	B	Formula
307410	H	CN	N	CH	C ₁₆ H ₁₀ BrN ₃ O ₂ S
307411	H	SO2NHEt	CH	N	C ₁₇ H ₁₆ BrN ₃ O ₄ S ₂
307412	-SCH2CH2O-		N	CH	C ₁₇ H ₁₃ BrN ₂ O ₃ S ₂

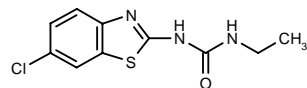
SOURCE – Eisai.

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1. Haneda, T. et al. (Eisai Co., Ltd.) *Heterocyclic cpds. having sulfonamide groups*. WO 0147891.

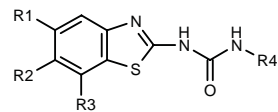
308459

N-(6-Chlorobenzothiazol-2-yl)-N'-ethylurea



C10 H10 Cl N3 O S; Mol wt: 255.7280

ACTION – An inhibitor of serine/threonine and tyrosine kinases, particularly tyrosine kinases involved in angiogenic and/or edematous processes such as KDR, Lck, Flt-1, VEGFR-3, FGFR, PDGFR, c-Met, Tie2, Tie1 or IGF-1R, with potential for the treatment of angiogenic, hyperproliferative and immunological disorders, among others. Other exemplified compounds from this series of 2-benzothiazolyl urea derivatives include the following:



Compound	R1	R2	R3	R4	Formula
308460	H	NO2	H	1-CO2Et-4-Pip	C ₁₆ H ₁₉ N ₅ O ₅ S
308461	H	NO2	H	cyclobutyl	C ₁₂ H ₁₂ N ₄ O ₃ S
308462	H	Cl	H	(CH2)5CO2Et	C ₁₆ H ₂₀ ClN ₃ O ₃ S
308464	H	H	i-PrO	Et	C ₁₃ H ₁₇ N ₃ O ₂ S
308466	H	3-Me-PhNHCO-NHCH2CH2CO	H	Et	C ₂₁ H ₂₃ N ₅ O ₃ S
308468	H	Br	H	3(R),5(S)-(Me)2-1-Piz-CO(CH2)3	C ₁₈ H ₂₄ BrN ₅ O ₂ S
308470	H	4-Me-1-Piz-(CH2)3NHCO	H	Et	C ₁₉ H ₂₈ N ₆ O ₂ S
308473	OMe	OMe	H	Et	C ₁₂ H ₁₅ N ₃ O ₃ S

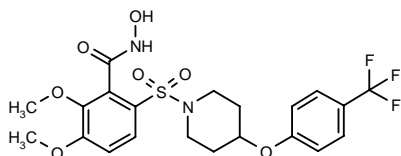
SOURCE – BASF.

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1. Cusack, K.P. et al. (BASF AG) *2-Benzothiazolyl urea derivs. and their use as protein kinase inhibitors*. WO 0157008.

308568

2,3-Dimethoxy-6-[4-[4-(trifluoromethyl)phenoxy]piperidin-1-ylsulfonyl]benzohydroxamic acid



C21 H23 F3 N2 O7 S; Mol wt: 504.4797

ACTION – Orally active matrix metalloproteinase (MMP) inhibitor selective for gelatinase A (MMP-2; IC_{50} = 2.4 nM) and collagenase 3 (MMP-13; IC_{50} = 2.7 nM) over interstitial collagenase (MMP-1; IC_{50} > 100 μ M). Compound exhibited good pharmacokinetic properties in rats with a C_{max} of 22.5 μ g/ml, $t_{1/2}$ of 1.9 h and an oral bioavailability of 32%. Potentially useful as an antiarthritic and anti-angiogenic agent.

SOURCE – Pharmacia.

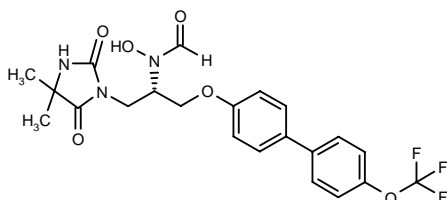
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3. Barta, T.E. et al. *Selective, orally active MMP inhibitor with an aryl backbone*. Bioorg Med Chem Lett 2001, 11(18): 2481.

ABT-770

307653

N-[2-(4,4-Dimethyl-2,5-dioximidazolidin-1-yl)-1(S)-[4'-(trifluoromethoxy)biphenyl-4-yloxymethyl]ethyl]-N-hydroxyformamide



C22 H22 F3 N3 O6; Mol wt: 481.4248

ACTION – Antineoplastic agent, a potent matrix metalloproteinase (MMP) inhibitor selective for gelatinase A (MMP-2; IC_{50} = 4 nM) over interstitial collagenase (MMP-1; IC_{50} = 4600 nM) and matrilysin (MMP-7; IC_{50} > 10,000 nM), and with lower activity against stromelysin 1 (MMP-3; IC_{50} = 42 nM) and gelatinase B (MMP-9; IC_{50} = 120 nM). Compound is orally bioavailable (F = 83 and

95% in dogs and monkeys, respectively), and showed efficacy in *in vivo* models of tumor growth: in mice bearing murine melanoma B16, it inhibited tumor growth at doses of 10-100 mg/kg p.o. and exhibited an additive effect in combination with paclitaxel.

SOURCE – Abbott.

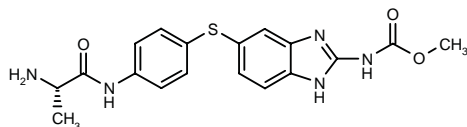
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2. Dai, Y. et al. (Abbott Laboratories Inc.) *N-Hydroxyformamide derivs. as inhibitors of matrix metalloproteinases*. US 6235786, WO 0044712.
3. Curtin, M.L. et al. *Discovery and characterization of the potent, selective and orally bioavailable MMP inhibitor ABT-770*. Bioorg Med Chem Lett 2001, 11(12): 1557.
4. Kurukulasuriya, R. et al. *Novel and scalable process to a matrix metalloproteinase inhibitor, ABT-770*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst ORGN-161.

ANG-615

301748

N-[5-[4-(L-Alanylamino)phenylsulfanyl]-1H-benzimidazol-2-yl]carbamic acid methyl ester



C18 H19 N5 O3 S; Mol wt: 385.4461

ACTION – Tumor vascular targeting and tubulin-binding agent, a benzimidazole carbamate proven to almost completely reduce breast adenocarcinoma CaNT tumor vasculature volumen (99% reduction at 50 mg/kg i.p.), and induce extensive tumor necrosis in mice. Compound showed a good solubility profile, suitable for simple formulation for i.v. administration.

SOURCE – Angiogene Pharmaceuticals.

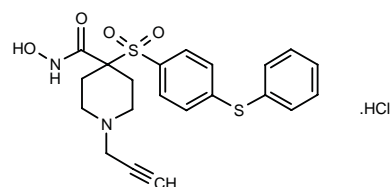
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SC-276*

294276

4-[4-(Phenylsulfanyl)phenylsulfonyl]-1-(2-propynyl)-piperidine-4-carboxylic acid hydrochloride



C21 H22 N2 O4 S2 . HCl; Mol wt: 467.0077

ACTION – Antiangiogenic agent, a potent and orally active matrix metalloproteinase (MMP) inhibitor with selectivity for gelatinase A (MMP-2; IC_{50} = 0.2 nM) and collagenase 3 (MMP-13; IC_{50} = 0.3 nM) over interstitial collagenase (MMP-1; IC_{50} = 9000 nM) and matrilysin (MMP-7; IC_{50} > 10,000 nM). Compound showed excellent efficacy in mice in a corneal micropocket angiogenesis model and in tumor xenograft models, where it dose-dependently decreased the growth of human breast HAL and human prostate PC-3 tumors. Furthermore, compound showed an additive effect when combined with cisplatin in a PC-3 xenograft model in mice.

SOURCE – Pharmacia.

REFERENCES

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3. Barta, T.E. et al. (Pharmacia Corp.) *Aromatic sulfone hydroxamic acid metalloprotease inhibitor*. WO 9925687.
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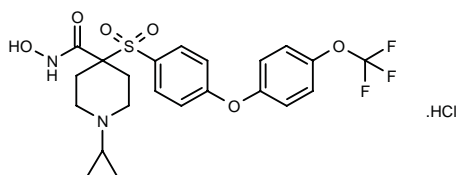
*Identified compound **294276** Drug Data Rep 2001, 023(02): 0190.

SC-77964

302539

1-Cyclopropyl-5-[4-[4-(trifluoromethoxy)phenoxy]phenylsulfonyl]piperidine-3-carboxylic acid hydrochloride

SC-964



C22 H23 F3 N2 O6 S . HCl; Mol wt: 536.9526

ACTION – Potent and selective matrix metalloproteinase (MMP) inhibitor with subnanomolar potency (IC_{50} < 0.1–0.2 nM) for MMP-2 (gelatinase A), MMP-8 (neutrophil collagenase), MMP-9 (gelatinase B) and MMP-13 (collagenase 3), while exhibiting less activity against MMP-1 (fibroblast collagenase; IC_{50} = 4000 nM). It dose-dependently inhibited angiogenesis in a mouse corneal micropocket assay and it produced significant inhibition of tumor growth in mice bearing human prostate adenocarcinoma PC-3, human lung carcinoma SK-MES and human breast cancer MDA-MB-435 and MX-1 xenografts. Moreover, it showed additive efficacy in combination with cisplatin or gemcitabine in the SK-MES lung cancer model. Potentially useful for the treatment of lung, prostate and breast cancers.

SOURCE – Pharmacia.

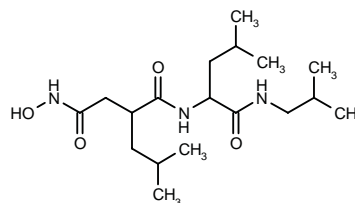
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3. Barta, T.E. et al. (Pharmacia Corp.) *Aromatic sulfone hydroxamic acid metalloprotease inhibitor*. WO 9925687.
4. McKearn, J.P. et al. (Pharmacia Corp.) *Method of using a cyclooxygenase-2 inhibitor and a matrix metalloproteinase inhibitor as a combination therapy in the treatment of neoplasia*. WO 0037107, WO 0038717, WO 0038718, WO 0038719, WO 0038730, WO 0038786.
5. Becker, D.P. et al. *Design and synthesis of potent orally active MMP-1 sparing matrix metalloproteinase inhibitors with efficacy in antitumor models*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 18.
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SI-27*

261873

2-[2-(*N*-Hydroxycarbamoylmethyl)-4-methylpentan-amido]-*N*-isobutyl-4-methylpentanamide



C18 H35 N3 O4; Mol wt: 357.4915

ACTION – Matrix metalloproteinase (MMP) inhibitor active against gelatinase A (MMP-2), gelatinase B (MMP-9), stromelysin 1 (MMP-3), bacterial collagenase, thermolysin and aminopeptidase M (IC_{50} = 0.036, 0.090, 0.17, 0.90, 0.27 and 15 μ M, respectively), with no activity against other proteases including trypsin, chymotrypsin, papain, pepsin and elastase. Compound was found to induce apoptosis in several human myeloid leukemia cell lines including U-937, NB4 and HL-60 cells, by a mechanism that involves activation of caspases 3, 8 and 9. Furthermore, at lower concentrations not directly inducing apoptosis, SI-27 sensitized U-937, HL-60 and NB4 cells to TNF- α -mediated apoptosis by a mechanism that involved blockade of NF- κ B activation through the cleavage of I κ B α . Potentially useful for the treatment of acute myeloid leukemia refractory to classical anticancer drugs.

SOURCE – Banyu.

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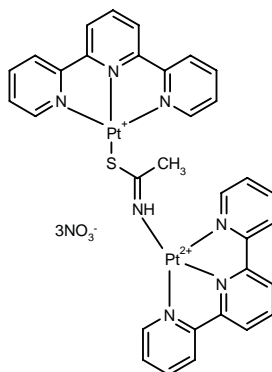
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2. Nakamura, Y. et al. *A new matrix metalloproteinase inhibitor SI-27 induces apoptosis in several human myeloid leukemia cell lines and enhances sensitivity to TNF α -induced apoptosis*. Leukemia 2001, 15(8): 1217.

*Identified compound **261873** Drug Data Rep1998, 020(05): 0447.

DNA-INTERCALATING DRUGS

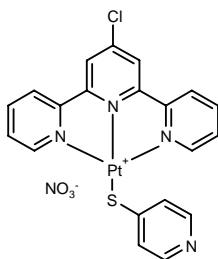
306615

[μ -(Ethanethioamidato- $\kappa N:\kappa S$)]bis(2,2':6',2''-terpyridine- $\kappa N^1,\kappa N^1',\kappa N^1''$)diplatinum(3+) trinitrate



C32 H26 N10 O9 Pt2 S; Mol wt: 992.8364

ACTION – Antineoplastic agent, a platinum complex proven to strongly inhibit the proliferation of the highly malignant glioma cell lines NCH37, NCH82 and NCH 89 (IC_{50} = 5.7, 3.9 and 2.5 μ M, respectively) and the head and neck squamous carcinoma cell lines HNO97 and HNO199 (IC_{50} = 4.8 and 6.2 μ M, respectively). The complex showed DNA-intercalating activity and inhibited thioredoxin reductase with a K_i of 4 nM for competitive inhibition and an IC_{50} of 2 nM for tight-binding inhibition. Furthermore, it exhibited high specificity over the closely related enzyme human glutathione reductase (30% inhibition at 10 μ M). Another related compound is:



306614: C20 H14 Cl N4 Pt S

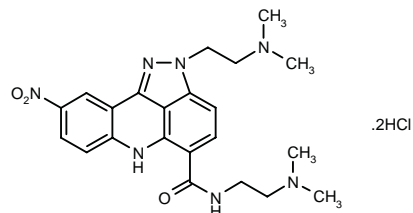
SOURCE – Isis Innovation.

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2. Becker, K. et al. *Human thioredoxin reductase is efficiently inhibited by (2,2':6',2''-terpyridine)platinum(II) complexes. Possible implications for a novel antitumor strategy.* J Med Chem 2001, 44(17): 2784.

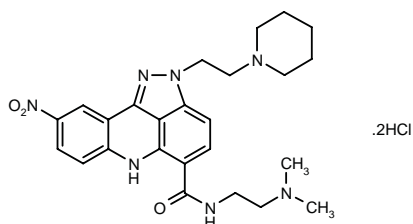
308030

N,2-Bis[2-(dimethylamino)ethyl]-9-nitro-2,6-dihydro-pyrazolo[3,4,5-*k*]acridine-5-carboxamide dihydrochloride



C22 H27 N7 O3 . 2HCl; Mol wt: 510.4231

ACTION – Antineoplastic agent, a DNA-intercalating agent with strong cytotoxic activity against human colon adenocarcinoma HT-29 cells (IC_{50} = 3.9 nM). Another related compound is:



308031: C25 H31 N7 O3 . 2HCl

SOURCE – Università degli Studi di Camerino, Camerino (IT).

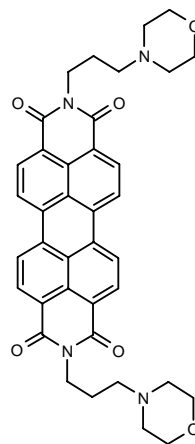
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TEL-01

307673

2,9-Bis[3-(4-morpholinyl)propyl]anthra[2,1,9-*def*:6,5,10-*d'e'f'*]diisoquinoline-1,3,8,10(2*H*,9*H*)-tetrone



C38 H36 N4 O6; Mol wt: 644.7244

ACTION – Telomerase inhibitor with pH-dependent selectivity for G-quadruplex DNA binding relative to double-stranded DNA binding. Potentially useful as a selective anticancer agent.

SOURCE – University of Texas System, Austin, TX (US).

REFERENCES

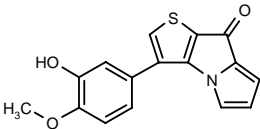
1. Kerwin, S.M. et al. (University of Texas System) *Inhibition of human telomerase by a G-quadruplex-interaction cpd.* US 6156763, WO 9940087.

2. Kerwin, S.M. et al. *G-quadruplex DNA binding selectivity of perylenetetracarboxylic acid diimides is pH dependent and mediated by ligand aggregation.* 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 142.

ANTIMITOTIC DRUGS

306972

3-(3-Hydroxy-4-methoxyphenyl)-8*H*-thieno[2,3-*b*]-pyrrolizin-8-one



C16 H11 N O3 S; Mol wt: 297.3329

ACTION – Antimitotic agent able to inhibit microtubule assembly (IC₅₀ = 2.9 μM) and to produce accumulation of 86% cells at the G2/M phase of the cell cycle. Compound showed broad-spectrum antiproliferative activity against cancer cell lines including human ovarian carcinoma OVCAR-3 cells (IC₅₀ = 0.031 μM), human small cell lung carcinoma H-69 cells (IC₅₀ = 0.036 μM) and human epidermoid carcinoma KB-3-1 and multidrug-resistant KB-A1 cells (IC₅₀ = 0.018 and 0.015 μM, respectively).

SOURCE – Servier.

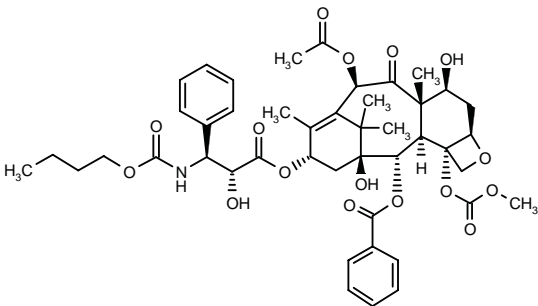
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1. Rault, S. et al. (ADIR et Cie.) *Derivs. of the 8H-(2,3-b)-pyrrolizine-8-one, process for their preparation and pharmaceutical compsns. containing them.* EP 0982308, FR 2781482, JP 2000044572, US 6071945.

2. Lisowski, V. et al. *Design, synthesis and antiproliferative activity of tripentones: A new series of antitubulin agents.* Bioorg Med Chem Lett 2001, 11(16): 2205.

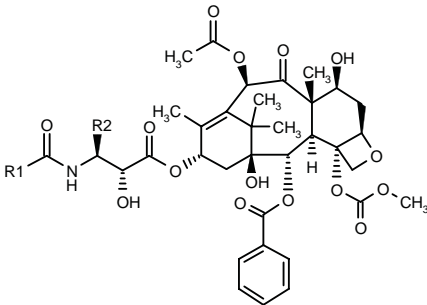
308486

3'-*N*-(Butoxycarbonyl)-4-*O*-deacetyl-3'-*N*-debenzoyl-4-*O*-(methoxycarbonyl)paclitaxel



C45 H55 N O16; Mol wt: 865.9205

ACTION – Antitumor agent with good oral bioavailability and good oral efficacy, proven active against human ovarian carcinoma A2780 xenografts implanted s.c. in nude mice when given at 100 mg/kg p.o. every 2 days x 5. Other specifically claimed compounds from this series of C-4 methyl carbonate taxane derivatives are:



Compound	R1	R2	Formula
308489	t-BuCH2	Ph	C ₄₆ H ₅₇ NO ₁₅
308490	cyclobutyl	Ph	C ₄₅ H ₅₃ NO ₁₅
308492	cyclohexyl-O	t-Bu	C ₄₅ H ₆₁ NO ₁₆
308494	t-BuCH2	t-Bu	C ₄₄ H ₆₁ NO ₁₅
308496	cyclobutyl	t-Bu	C ₄₃ H ₅₇ NO ₁₅
308498	2-furyl	t-Bu	C ₄₃ H ₅₃ NO ₁₆
308534	t-BuO	t-Bu	C ₄₃ H ₅₉ NO ₁₆
308536	t-BuO	i-Pr	C ₄₂ H ₅₇ NO ₁₆
308537	t-BuO	Ph	C ₄₅ H ₅₅ NO ₁₆

SOURCE – Bristol-Myers Squibb.

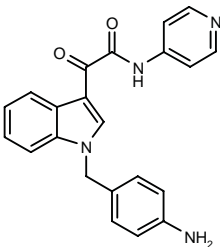
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1. Kadow, J.F. et al. (Bristol-Myers Squibb Co.) *C-4 carbonate taxanes.* WO 0156565.

D-68838

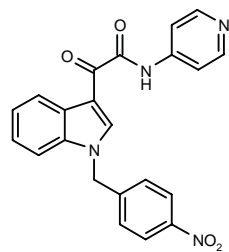
307734

2-[1-(4-Aminobenzyl)-1*H*-indol-3-yl]-2-oxo-*N*-(4-pyridyl)-acetamide



C22 H18 N4 O2; Mol wt: 370.4102

ACTION – Antineoplastic agent that acts by inhibiting tubulin polymerization, thereby causing microtubule destabilization. Another specifically claimed compound from this series of substituted *N*-benzylindol-3-ylglyoxylic acid derivatives is:



D-68836 [307735]: C22 H16 N4 O4

SOURCE – Asta Medica.

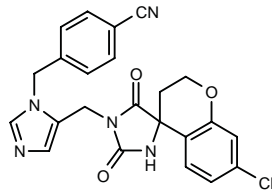
REFERENCES

1. Günther, E. et al. (Asta Medica AG) *Substd. N-benzyl-indol-3-yl glyoxylic acid derivs. having an anti-tumoral effect.* DE 19962300, WO 0147913.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

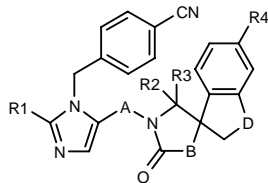
307672

4-[5-(7-Chloro-2',5'-dioxospiro[3,4-dihydro-2H-1-benzopyran-4,4'-imidazolidin]-1'-ylmethyl)-1H-imidazol-1-ylmethyl]benzonitrile



C23 H18 Cl N5 O3; Mol wt: 447.8802

ACTION – An inhibitor of protein prenyltransferases, particularly protein farnesyltransferase, and the prenylation of the oncogene protein Ras, with potential in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, as well as for conferring radiation sensitivity to tumor cells. Other specifically claimed compounds from this series of spiro derivatives are:



Compound	R1	R2	R3	R4	A	B	D	Formula
307684	Me	-O-		Cl	-(CH2)2-	NH	-CH2O-	C ₂₅ H ₂₂ ClN ₅ O ₃
307686	H	H	H	Cl	-CH2-	O	-CH2-	C ₂₃ H ₁₉ ClN ₅ O ₂
307687	H	-O-		F	-CH2-	NH	-CH2-	C ₂₃ H ₁₈ FN ₅ O ₂

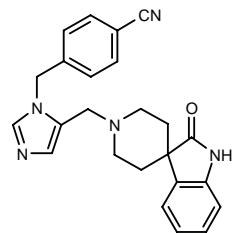
SOURCE – Merck & Co.

REFERENCES

1. Hoffman, J.M. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase.* WO 0145704.

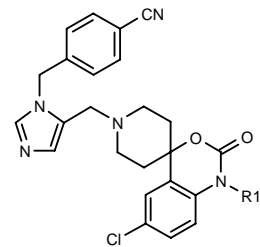
307688

4-[5-[2-Oxospiro[indoline-3,4'-piperidin]-1'-ylmethyl]-1H-imidazol-1-ylmethyl]benzonitrile



C24 H23 N5 O; Mol wt: 397.4797

ACTION – An inhibitor of protein prenyltransferases, particularly protein farnesyltransferase, and the prenylation of the oncogene protein Ras, with potential in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, as well as for conferring radiation sensitivity to tumor cells. Other specifically claimed compounds from this series of spiro derivatives are:



Compound	R1	Formula
307689	H	C ₂₄ H ₂₂ ClN ₅ O ₂
307690	CH2CF3	C ₂₆ H ₂₃ ClF ₃ N ₅ O ₂
307692	Bu	C ₂₈ H ₃₀ ClN ₅ O ₂
307693	3-(CF3O)-PhCH2	C ₃₂ H ₂₇ ClF ₃ N ₅ O ₃

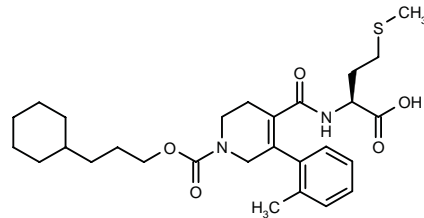
SOURCE – Merck & Co.

REFERENCES

1. Hoffman, J.M. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase.* WO 0145707.

308065

N-[1-(3-Cyclohexylpropoxycarbonyl)-5-(2-methylphenyl)-1,2,3,6-tetrahydropyridin-4-ylcarbonyl]-L-methionine



C28 H40 N2 O5 S; Mol wt: 516.6990

ACTION – A representative compound from a series of tetrahydropyridine-4-carboxamide derivatives that inhibits protein isoprenyltransferases, as demonstrated by 100% inhibition of rat brain protein farnesyltransferase at 0.1 µM. Potentially useful for the treatment of cancer, as well as the prevention of intimal hyperplasia associated with restenosis and atherosclerosis.

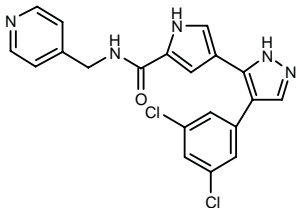
SOURCE – Abbott.

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1. O'Connor, S.J. and Nelson, L.T.J. (Abbott Laboratories Inc.) *Inhibitors of protein isoprenyl transferases*. US 6277871.

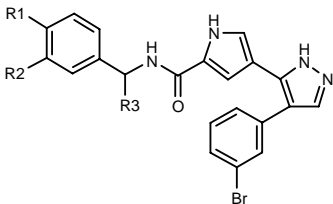
308087

4-[4-(3,5-Dichlorophenyl)-1H-pyrazol-5-yl]-N-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide



C20 H15 Cl2 N5 O; Mol wt: 412.2785

ACTION – An inhibitor of protein kinases such as ERK2 ($K_i < 1 \mu\text{M}$), JNK ($K_i < 1 \mu\text{M}$), Aurora2 ($\text{IC}_{50} < 5 \mu\text{M}$) and KDR ($> 40\%$ inhibition at $2 \mu\text{M}$), potentially useful for the treatment of a broad range of disorders, particularly cancer and cardiovascular disorders such as restenosis, atherosclerosis, myocardial infarction and congestive heart failure. Within this series of pyrazole derivatives, the following compounds are also included:



Compound	R1	R2	R3	Formula
308088	-OCH2CH2-		H	C ₂₃ H ₁₉ BrN ₄ O ₂
308090	H	H	CH2OH	C ₂₂ H ₁₉ BrN ₄ O ₂

SOURCE – Vertex.

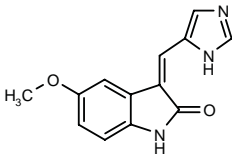
REFERENCES

1. Green, J. et al. (Vertex Pharmaceuticals Inc.) *Pyrazole compsns. useful as inhibitors of ERK*. WO 0157022.

SU-9516

287425

(Z)-3-(1H-Imidazol-5-ylmethylene)-5-methoxy-2,3-dihydro-1H-indol-2-one



C13 H11 N3 O2; Mol wt: 241.2489

ACTION – Antineoplastic agent, a cyclin-dependent kinase CDK2 inhibitor ($\text{IC}_{50} = 22 \text{ nM}$), with 1.8-fold selectivity over CDK1 ($\text{IC}_{50} = 40 \text{ nM}$), 9-fold selectivity over CDK4 ($\text{IC}_{50} = 9.2 \mu\text{M}$) and > 450 -fold selectivity over other kinases. Compound decreased CDK2-specific phosphorylation of pRB in human colon carcinoma RKO cells, and both CDK2- and CDK4-specific pRB phosphorylation in human colon carcinoma SW480 cells. In asynchronous SW480 and RKO cells, it inhibited cell cycle progression, producing cell cycle arrest in the G2/M phase; however, in serum-deprived cells, compound blocked cell cycle in the G0/G1 phase in SW480 cells, but not in RKO cells. Furthermore, long-term exposure (24, 48 or 72 h) of both RKO and SW480 cells to compound was associated with increased apoptosis. Compound showed antiproliferative activity against human epidermoid carcinoma A-431, colorectal adenocarcinoma COLO 205, non-small cell lung carcinoma NCI-H460, RKO and SW480 cell lines ($\text{IC}_{50} = 2.2$ - $6.4 \mu\text{M}$), as well as against epidermal growth factor (EGF)-, platelet-derived growth factor (PDGF)- and insulin-like growth factor (IGF-I)-stimulated murine 3T3 fibroblasts ($\text{IC}_{50} = 3.2$ - $7.9 \mu\text{M}$).

SOURCE – Sugen (Pharmacia).

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1. Flocco, M.M. et al. *Different binding modes of two structurally similar CDK2 inhibitors*. Proc Amer Assoc Cancer Res 2001, 42: Abst 4461.0

2. Huang, P. et al. *Novel indolinone compounds as potent cyclin-dependent kinase 2 inhibitors*. Proc Amer Assoc Cancer Res 2001, 42: Abst 3622.

3. Lane, M.E. et al. *A novel cdk2-selective inhibitor, SU9516, induces apoptosis in colon carcinoma cells*. Cancer Res 2001, 61(16): 6170.

4. lane, M.E. et al. *Combined adenovirus DI1520 and SU9516 therapy produces a synergistic response in human colon carcinoma cells*. Proc Am Soc Clin Oncol 2000, 19: Abst 1875.

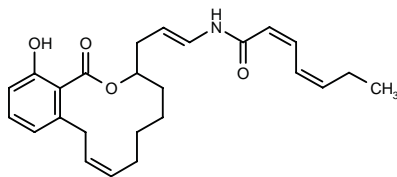
5. Lane, M.E. et al. *Effects of CDK inhibitor SU9516 on human colon cancer cells*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1586.

6. Yu, B. et al. *Inhibition of cyclin dependent kinase 2 (CDK2) by SU9516 prevents dissociation of retinoblastoma protein (pRb) from E2F*. Proc Amer Assoc Cancer Res 2001, 42: Abst 714.

OTHER ONCOLYTIC DRUGS

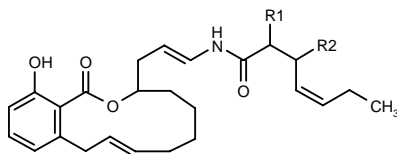
307681

N-[3-[(*Z*)-14-Hydroxy-1-oxo-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-3-yl]-1(*E*)-propenyl]-2(*Z*),4(*Z*)-heptadienamide



C25 H31 N O4; Mol wt: 409.5229

ACTION – Antineoplastic agent, a salicylihalamide A analogue with good cytotoxic potency against a range of tumor cells including human breast cancer MCF-7 (IC₅₀ = 0.4 μM) and human non-small cell lung cancer H-460 cells (IC₅₀ = 0.1 μM). Other salicylihalamide analogues are:



Compound	R1	R2	Formula
307682	bond		C ₂₅ H ₃₁ NO ₄
307683	H	H	C ₂₅ H ₃₃ NO ₄

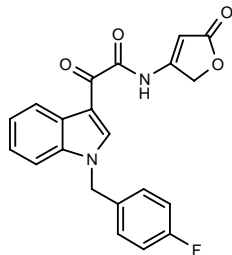
SOURCE – Shire BioChem.

REFERENCES

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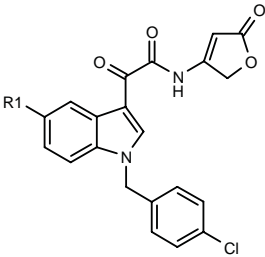
307740

2-[1-(4-Fluorobenzyl)-1*H*-indol-3-yl]-2-oxo-*N*-(5-oxo-2,5-dihydrofuran-3-yl)acetamide



C21 H15 F N2 O4; Mol wt: 378.3575

ACTION – Antitumor agent particularly useful for the treatment of solid tumors including colon and lung cancer. It displayed IC₅₀ values of 0.0004, 0.035, 0.012 and 0.088 μg/ml, respectively, against the human cancer cell lines HT-29 (colon), PC-3 (prostate), H-460M (lung) and MKN-45 (gastric). Other exemplified 2-indolyl-2-oxoacetamides are:



Compound	R1	Formula
307741	H	C ₂₁ H ₁₅ ClN ₂ O ₄
307742	Cl	C ₂₁ H ₁₄ Cl ₂ N ₂ O ₄

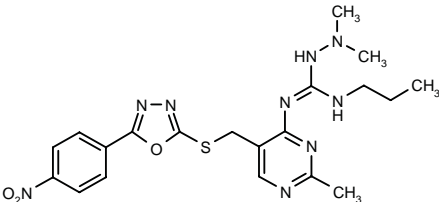
SOURCE – Novuspharma.

REFERENCES

1. Menta, E. and Pescalli, N. (Novuspharma SpA) *2-(1*H*-Indol-3-yl)-2-oxo-acetamides with antitumor activity*. WO 0147916.

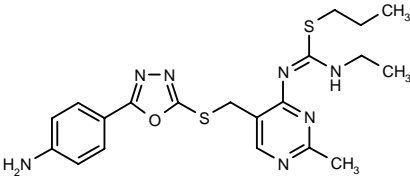
308085

1-(Dimethylamino)-2-[2-methyl-5-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-ylsulfanylmethyl]pyrimidin-4-yl]-3-propyl-guanidine



C20 H25 N9 O3 S; Mol wt: 471.5435

ACTION – Antitumor agent particularly useful for the treatment of solid tumors such as pancreatic, colon and lung cancers. It inhibited the proliferation of several human cancer cells including non-small cell lung carcinoma A549 (IC₅₀ = 51.4 ng/ml), colon carcinoma HT-29 (IC₅₀ = 0.4 ng/ml), squamous cell lung cancer Ma44 and RERF-LC-A1 (IC₅₀ = 0.4 ng/ml), and lung carcinoma H460 (27.5 ng/ml). Another exemplified pyrimidine derivative is:



308086: C20 H25 N7 O S2

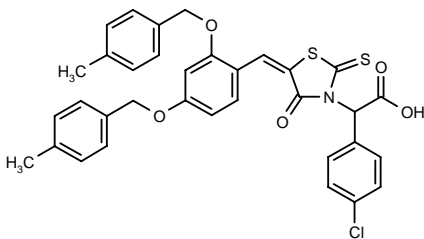
SOURCE – Shionogi.

REFERENCES

1. Tanaka, H. et al. (Shionogi & Co. Ltd.) *Pyrimidine derivs. having antitumor effect*. WO 0151488.

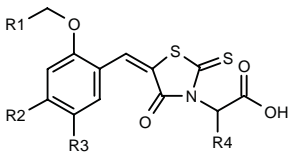
308110

2-[5-[2,4-Bis(4-methylbenzyloxy)benzylidene]-4-oxo-2-thioxothiazolidin-3-yl]-2-(4-chlorophenyl)acetic acid



C34 H28 Cl N O5 S2; Mol wt: 630.1822

ACTION – Urokinase inhibitor that inhibits the binding of urokinase-type plasminogen activator (uPA) to its specific cell-surface receptor uPAR, as demonstrated *in vitro* (69% inhibition at 1 µg/ml). Potentially useful for the prevention of tumor growth and metastasis. Other specifically claimed thiazolidine-carboxylic acids are:



Compound	R1	R2	R3	R4	Formula
308112	4-Me-Ph	4-Me-Ph-CH2O	H	H	C ₂₈ H ₂₅ NO ₅ S ₂
308113	4-Me-Ph	H	4-Me-Ph-CH2O	H	C ₂₈ H ₂₅ NO ₅ S ₂
308114	4-Cl-Ph-CH2CH2	H	4-Cl-Ph-(CH2)3O	H	C ₃₀ H ₂₇ Cl ₂ NO ₅ S ₂
308115	Ph	H	O(CH2)3Ph	H	C ₂₈ H ₂₅ NO ₅ S ₂
308116	2-thienyl	H	O(CH2)3Ph	H	C ₂₆ H ₂₃ NO ₅ S ₃
308118	4-Me-Ph	4-Me-Ph-CH2O	H	Ph	C ₃₄ H ₂₉ NO ₅ S ₂
308119	4-Me-Ph	4-Me-Ph-CH2O	H	CH2Ph	C ₃₅ H ₃₁ NO ₅ S ₂

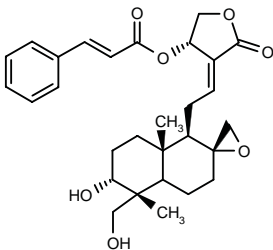
SOURCE – Roche.

REFERENCES

1. Friebe, W.-G. et al. (F. Hoffmann-La Roche AG) *Thiazolidine carboxylic acid derivs. and their use in the treatment of cancer*. WO 0157006.

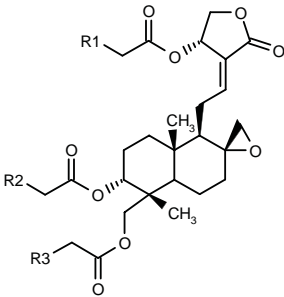
308321

3-Phenyl-2-propenoic acid 4-[2-[(1*R*,2*R*,5*R*,3*R*,6*R*,8*aS*)-6-hydroxy-5-(hydroxymethyl)-5,8*a*-dimethylspiro[perhydronaphthalene-2,2'-oxiran]-1-yl]ethylidene]-5-oxotetrahydrofuran-3(*S*)-yl ester



C29 H36 O7; Mol wt: 496.5964

ACTION – Andrographolide derivative active *in vitro* against a variety of human cancer cell lines and proven to inhibit HIV by 68% at 1 µM; at the same concentration, this compound also stimulated human lymphocyte proliferation. In addition, it reduced plasma triglyceride levels and body weight by 42 and 29%, respectively, when administered to mice at a dose of 100 mg/kg orally. Potentially useful for the treatment of cancer, psoriasis, restenosis, atherosclerosis, viral infections including HSV and HIV, malaria, bacterial infections, hepatic and cardiovascular disorders, diabetes, dyslipidemia and other metabolic disorders. Other exemplified compounds are:



Compound	R1	R2=R3	Formula
308322	H	H	C ₂₆ H ₃₆ O ₉
308323	t-BuOCONH	Me	C ₃₃ H ₄₉ NO ₁₁

SOURCE – Dr. Reddy’s Research Foundation.

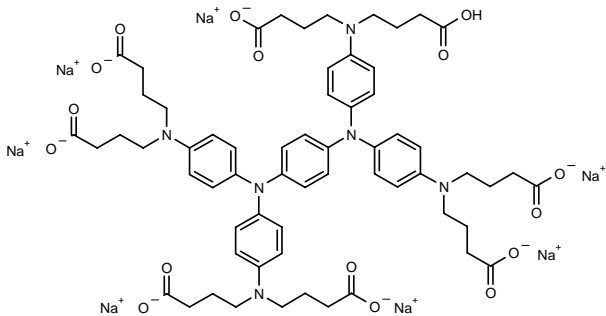
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1. Nanduri, S. et al. (Dr. Reddy’s Research Foundation) *Cpds. having antitumor activity: Process for their preparation and pharmaceutical compsns. containing them*. WO 0157026.

RADIATION THERAPY

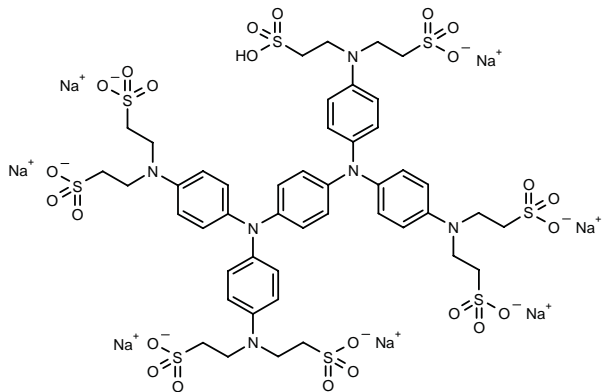
308261

8-Cascade:phenylene-1,4-diamine[*N,N,N',N'*:(1,4-phenylene):(nitrido):butyric acid heptasodium salt



C62 H69 N6 Na7 O16; Mol wt: 1315.1830

ACTION – Agent for photochemical therapy proven to induce necrosis of human colon cancer DLD-1 xenografts when given to mice intratumorally (15 mg/kg) accompanied by laser radiation to the tumor site. In addition, it exerted blockade of blood flow following s.c. and intratumoral administration to irradiated mice. Potentially useful in the treatment of cancer, thrombosis, arteriosclerosis, circulatory diseases, etc. Another exemplified aminium compound is:



308262: C46 H53 N6 Na7 O24 S8

SOURCE – Nippon Kayaku.

REFERENCES

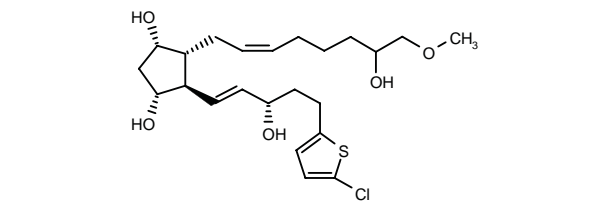
1. Yokumoto, H. et al. (Nippon Kayaku Co., Ltd.) *Novel aminium cpds.* JP 2001181248.

OCULAR MEDICATIONS

305571

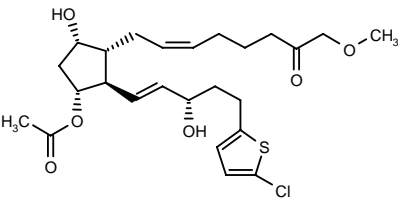
4(R)-[5-(5-Chlorothien-2-yl)-3(S)-hydroxy-1(E)-pentenyl]-5(R)-[7-hydroxy-8-methoxy-2(Z)-octenyl]cyclopentane-1(S),3(R)-diol

17-(5-Chlorothien-2-yl)-1-deoxo-1-(methoxymethyl)-18,19,20-trinorprostaglandin F_{2α}



C23 H35 Cl O5 S; Mol wt: 459.0435

ACTION – Agent for the management of glaucoma with potent ocular hypotensive activity, as demonstrated in dogs when administered at a concentration of 0.03% intraocularly. Another exemplified compound from this series of cyclopentane derivatives is:



305572: C25 H35 Cl O6 S

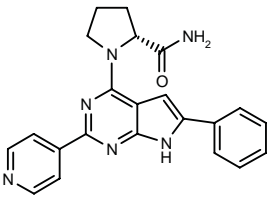
SOURCE – Allergan.

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1. Burk, R.M. et al. (Allergan, Inc.) *Cyclopentane 1-hydroxy alkyl or alkenyl-2-one or 2-hydroxy derivs. as therapeutic agents.* US 6248783.

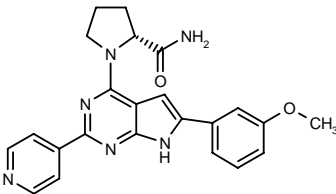
306310

1-[6-Phenyl-2-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]pyrrolidine-2(R)-carboxamide



C22 H20 N6 O; Mol wt: 384.4410

ACTION – Selective adenosine A₃ receptor antagonist with potential for the treatment of eye disorders including retinal or optic nerve damage, and preferably glaucoma. Another exemplified N⁶-substituted 7-deazapurine is:



306311: C23 H22 N6 O2

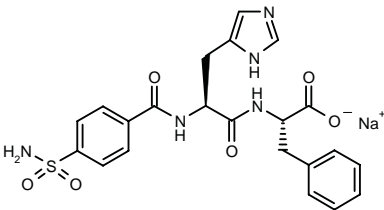
SOURCE – OSI Pharmaceuticals.

REFERENCES

1. Castelhano, A.L. et al. (OSI Pharmaceuticals, Inc.) *Cpds. specific to adenosine A₁, A_{2A}, and A₃ receptor and uses thereof.* WO 0139777.

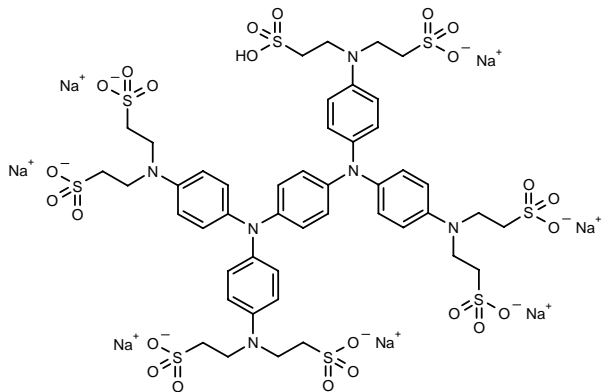
307667

N-(4-Sulfamoylbenzoyl)-L-histidyl-L-phenylalanine sodium salt



C22 H22 N5 Na O6 S ; Mol wt: 507.5008

ACTION – Agent for photochemical therapy proven to induce necrosis of human colon cancer DLD-1 xenografts when given to mice intratumorally (15 mg/kg) accompanied by laser radiation to the tumor site. In addition, it exerted blockade of blood flow following s.c. and intratumoral administration to irradiated mice. Potentially useful in the treatment of cancer, thrombosis, arteriosclerosis, circulatory diseases, etc. Another exemplified aminium compound is:



308262: C46 H53 N6 Na7 O24 S8

SOURCE – Nippon Kayaku.

REFERENCES

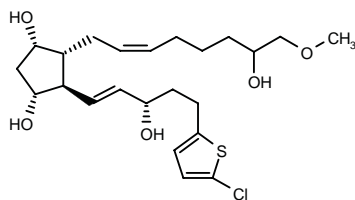
1. Yokumoto, H. et al. (Nippon Kayaku Co., Ltd.) *Novel aminium cpds.* JP 2001181248.

OCULAR MEDICATIONS

305571

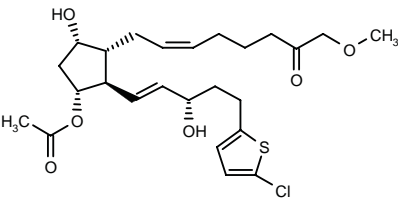
4(R)-[5-(5-Chlorothien-2-yl)-3(S)-hydroxy-1(E)-pentenyl]-5(R)-[7-hydroxy-8-methoxy-2(Z)-octenyl]cyclopentane-1(S),3(R)-diol

17-(5-Chlorothien-2-yl)-1-deoxo-1-(methoxymethyl)-18,19,20-trinorprostaglandin F_{2α}



C23 H35 Cl O5 S; Mol wt: 459.0435

ACTION – Agent for the management of glaucoma with potent ocular hypotensive activity, as demonstrated in dogs when administered at a concentration of 0.03% intraocularly. Another exemplified compound from this series of cyclopentane derivatives is:



305572: C25 H35 Cl O6 S

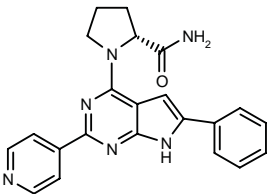
SOURCE – Allergan.

REFERENCES

1. Burk, R.M. et al. (Allergan, Inc.) *Cyclopentane 1-hydroxy alkyl or alkenyl-2-one or 2-hydroxy derivs. as therapeutic agents.* US 6248783.

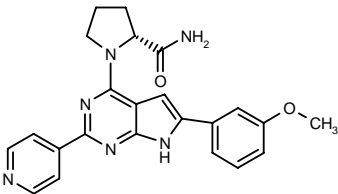
306310

1-[6-Phenyl-2-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]pyrrolidine-2(R)-carboxamide



C22 H20 N6 O; Mol wt: 384.4410

ACTION – Selective adenosine A₃ receptor antagonist with potential for the treatment of eye disorders including retinal or optic nerve damage, and preferably glaucoma. Another exemplified N⁶-substituted 7-deazapurine is:



306311: C23 H22 N6 O2

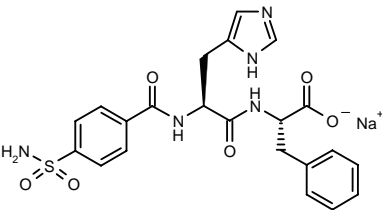
SOURCE – OSI Pharmaceuticals.

REFERENCES

1. Castelhano, A.L. et al. (OSI Pharmaceuticals, Inc.) *Cpds. specific to adenosine A₁, A_{2A}, and A₃ receptor and uses thereof.* WO 0139777.

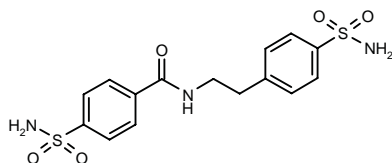
307667

N-(4-Sulfamoylbenzoyl)-L-histidyl-L-phenylalanine sodium salt

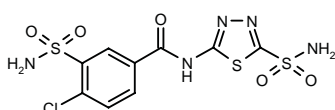


C22 H22 N5 Na O6 S ; Mol wt: 507.5008

ACTION – Topical antiglaucoma agent, a selective inhibitor of human carbonic anhydrase (CA) type II ($K_i = 9$ nM) over human CA I and bovine CA IV ($K_i = 240$ and 23 nM, respectively). Compound showed good water solubility and reduced intraocular pressure (IOP) in both normotensive and glaucomatous rabbits when given topically to the eye. Good efficacy and a prolonged duration of action were seen as compared to the clinically available dorzolamide and brinzolamide. Other related compounds are:



307668: C₁₅ H₁₇ N₃ O₅ S₂



307669: C₉ H₈ Cl N₅ O₅ S₃

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

1. Mincione, F. et al. *Carbonic anhydrase inhibitors: 4-Sulfamoyl-benzenecarboxamides and 4-chloro-3-sulfamoyl-benzenecarboxamides with strong topical antiglaucoma properties*. *Bioorg Med Chem Lett* 2001, 11(13): 1787.

EYE-001

264254

Octacosasodium salt of a 28-mer oligonucleotide aptamer whose sequence is:

5'-CGGAAUCAGUGAAUGCUUAUACAUCG-3'-3'-dT, in which all pyrimidine nucleotides are 2'-F-pyrimidines and all purine nucleotides are 2'-O-Me-purines, except adenines in positions 4 and 5 which are unmodified; it contains a deoxythymidine linked to the 3'-terminus via a 3'-3' linkage and a 40-kDa polyethylene glycol moiety conjugated via a linker to the 5'-terminus

NX-1838 (formerly)

ACTION – Single-stranded RNA oligonucleotide aptamer that inhibits vascular endothelial growth factor (VEGF). It specifically recognizes the VEGF₁₆₅ major soluble isoform and blocks its binding to human umbilical vein endothelial cells (HUVEC), as well as VEGF₁₆₅-induced Ca²⁺ mobilization and cell proliferation ($IC_{50} = 0.1-1$ nM). The oligonucleotide also prevented VEGF₁₆₅-mediated phosphorylation of KDR and phospholipase C γ . Pharmacokinetic and safety studies following injection into the vitreous humor of rhesus monkeys showed that it was well tolerated and was eliminated with a half-life of approximately 94 h; it was absorbed intact into the plasma compartment. Compound is undergoing phase II/III clinical trials for the treatment of age-related macular degeneration (AMD).

SOURCES – EyeTech; licensed from Gilead.

REFERENCES

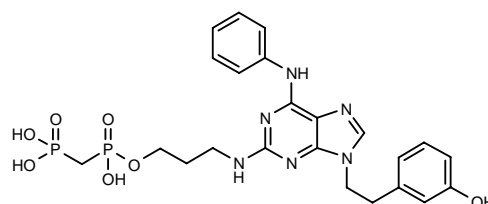
1. Bell, C. et al. *Oligonucleotide NX1838 inhibition of vascular endothelial growth factor (VEGF)-induced cellular responses in vitro*. *FASEB J* 1999, 13(4, Part 1): Abst 26.6.
2. Bell, C. et al. *Oligonucleotide NX1838 inhibits VEGF165-mediated cellular responses in vitro*. *In Vitro Cell Dev Biol Anim* 1999, 35(9): 533.
3. Drolet, D.W. et al. *Pharmacokinetics and safety of an anti-vascular endothelial growth factor aptamer (NX1838) following injection into the vitreous humor of rhesus monkeys*. *Pharm Res* 2000, 17(12): 1503.
4. Ruckman, J. et al. *2'-Fluoropyrimidine RNA-based aptamers to the 165-amino acid form of vascular endothelial growth factor (VEGF165)*. *J Biol Chem* 1998, 273(32): 20556.
5. Tomkinson, B. et al. *NX1838, a VEGF-specific antagonist aptamer, inhibits the growth of human xenografts in nude mice and enhances a sub optimal dose of Taxol*. *Proc Amer Assoc Cancer Res* 1999, 40: Abst 4097.
6. Tucker, C.E. et al. *Detection and plasma pharmacokinetics of an anti-vascular endothelial growth factor oligonucleotide-aptamer (NX1838) in rhesus monkeys*. *J Chromatogr B - Biomed Sci Appl* 1999, 732(1): 203.
7. *Company Profile: EyeTech Pharmaceuticals*. *DailyDrugNews.com* (Daily Essentials) 2001, Oct 9.
8. *First SELEX compound from NeXstar heads for clinical trials in ARMD*. *DailyDrugNews.com* (Daily Essentials) 1998, July 27.
9. *Gilead licenses NX-1838, a new AMD treatment, to EyeTech*. *DailyDrugNews.com* (Daily Essentials) 2000, April 10.
10. *IND application for NeXstar antiangiogenesis drug approved by FDA*. *DailyDrugNews.com* (Daily Essentials) 1998, Sept 4.
11. *NeXstar: Q1 1999 highlights*. *DailyDrugNews.com* (Daily Essentials) 1999, April 29.
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

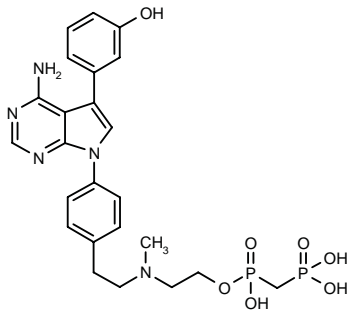
307113

[[3-[9-[2-(3-Hydroxyphenyl)ethyl]-N⁶-phenyl-9H-adenin-2-ylamino]propoxy](hydroxy)phosphorylmethyl]phosphonic acid

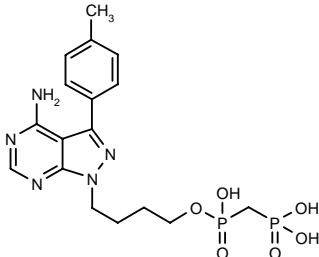


C₂₃ H₂₈ N₆ O₇ P₂; Mol wt: 562.4572

ACTION – Bone-targeted compound that specifically acts as an Src kinase inhibitor ($IC_{50} = 0.055$ μ M). Potentially useful for the treatment of bone disorders, preferably for inhibiting bone resorption. In a rabbit osteoclast assay, it produced 100% inhibition of bone resorption at 20 μ M. Other exemplified heterocyclic compounds are:



307115: C24 H29 N5 O7 P2



307116: C17 H23 N5 O6 P2

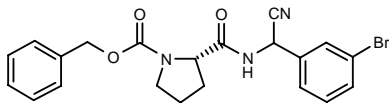
SOURCE – Ariad.

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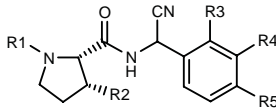
307822

*N*²-(Benzyloxycarbonyl)-*N*¹-[1-(3-bromophenyl)-1-cyanomethyl]-L-prolinamide

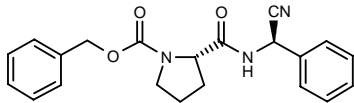


C21 H20 Br N3 O3; Mol wt: 442.3110

ACTION – Selective cathepsin K inhibitor with an IC₅₀ of 0.016 μM against cathepsin K versus an IC₅₀ > 10 μM against cathepsins S, L and B. Expected to be useful for the treatment of cysteine protease-mediated conditions, particularly osteoporosis, unstable angina pectoris and plaque rupture. Other exemplified nitrile derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
307826	CO2CH2Ph	Me	H	OMe	OMe	C ₂₄ H ₂₇ N ₃ O ₅
307827	CO2CH2Ph	H	H	-OCH2O-		C ₂₂ H ₂₁ N ₃ O ₅
307828	CO2CH2Ph	H	Me	H	H	C ₂₂ H ₂₃ N ₃ O ₃
307830	COCH2OCH2Ph	H	H	-OCH2O-		C ₂₃ H ₂₃ N ₃ O ₅
307831	cyclopentyl-CH2CH2CO	H	H	-OCH2O-		C ₂₂ H ₂₇ N ₃ O ₄
307832	CO2CH2Ph	H	H	OMe	OCH2Ph	C ₂₉ H ₂₉ N ₃ O ₅
307833	2-furyl-CH2NHCS	H	H	OMe	OMe	C ₂₁ H ₂₄ N ₄ O ₄ S
307836	3-Br-PhCH2CO	H	H	-OCH2O-		C ₂₂ H ₂₀ BrN ₃ O ₄
307837	3-Br-PhCH2CO	H	H	OMe	OMe	C ₂₃ H ₂₄ BrN ₃ O ₄
307839	4-Br-PhCH2CO	H	H	-OCH2O-		C ₂₂ H ₂₀ BrN ₃ O ₄



307825: C21 H21 N3 O3

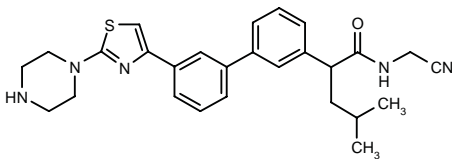
SOURCE – Roche.

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1. Gabriel, T. et al. (F. Hoffmann-La Roche AG) *Nitrile derivs. as cathepsin K inhibitors*. WO 0147886.

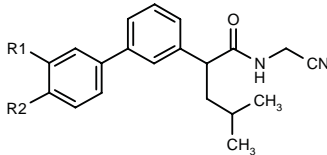
308015

N-(Cyanomethyl)-4-methyl-2-[3'-[2-(1-piperazinyl)thiazol-4-yl]biphenyl-3-yl]pentanamide

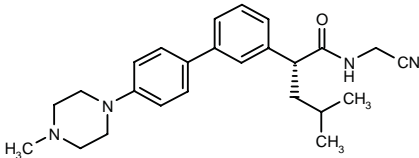


C27 H31 N5 O S; Mol wt: 473.6419

ACTION – Cathepsin inhibitor, particularly active against cathepsins B, K, L and S, with potential in a variety of cathepsin-mediated diseases, particularly osteoporosis in postmenopausal women. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
308017	2-pyrrolidinyl-CH2O	H	C ₂₅ H ₃₁ N ₃ O ₂
308018	3-pyrrolidinyl-O	H	C ₂₄ H ₂₉ N ₃ O ₂
308020	H	1-(HOCH2CH2)-4-Pip-O	C ₂₇ H ₃₆ N ₃ O ₃
308023	4-morpholinyl-CH2CH2NHCO	H	C ₂₇ H ₃₄ N ₄ O ₃
308025	4-(HOCH2CH2)-1-Piz-CO	H	C ₂₇ H ₃₄ N ₄ O ₃
308026	2-(1-Piz-CH2)-4-thiazolyl	H	C ₂₈ H ₃₃ N ₅ OS



308022: C21 H21 N3 O3

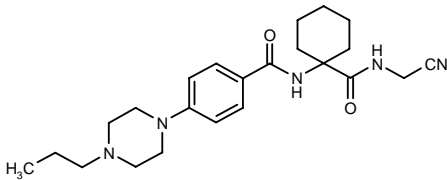
SOURCES – Axys Pharmaceuticals; Merck Frosst.

REFERENCES

1. Oballa, R.M. et al. (Merck Frosst Canada & Co.; Axys Pharmaceuticals, Inc.) *Novel cpds. and compns. as protease inhibitors*. WO 0149288.

308672

N-[1-[*N*-(Cyanomethyl)carbamoyl]cyclohexyl]-4-(4-propylpiperazin-1-yl)benzamide



C23 H33 N5 O2; Mol wt: 411.5467

ACTION – A representative compound from a series of cathepsin K inhibitors with potential in the treatment of cathepsin K-mediated diseases, particularly osteoporosis.

SOURCE – Novartis.

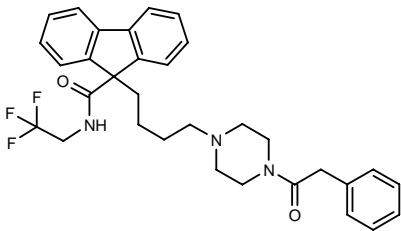
REFERENCES

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TREATMENT OF LIPOPROTEIN DISORDERS

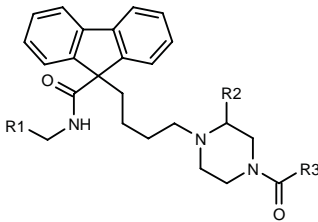
307851

9-[4-[4-(2-Phenylacetyl)piperazin-1-yl]butyl]-*N*-(2,2,2-trifluoroethyl)-9*H*-fluorene-9-carboxamide



C32 H34 F3 N3 O2; Mol wt: 549.6336

ACTION – Agent for the treatment of hyperlipidemia, atherosclerosis, diabetes mellitus, obesity and pancreatitis, an inhibitor of microsomal triglyceride transfer protein (MTP). Other specifically claimed compounds from this series of substituted piperazine derivatives are:



Compound	R1	R2	R3	Formula
307852	CF3	H	4-CF3-PhCH2	C ₃₃ H ₃₃ F ₆ N ₃ O ₂
307853	CF3	H	4-Br-PhCH2	C ₃₂ H ₃₃ BrF ₃ N ₃ O ₂
307854	CF3	H	NHCH2Ph	C ₃₂ H ₃₅ F ₃ N ₄ O ₂
307855	CF3	H	CH(Et)Ph	C ₃₄ H ₃₈ F ₃ N ₃ O ₂
307856	CF3	H	4-Cl-PhCH2	C ₃₂ H ₃₃ ClF ₃ N ₃ O ₂
307857	CF3	H	4-F-PhCH2	C ₃₂ H ₃₃ F ₄ N ₃ O ₂
307858	Ph	H	CH2Ph	C ₃₇ H ₃₉ N ₃ O ₂
307859	CF3	H	3-Cl-PhCH2	C ₃₂ H ₃₃ ClF ₃ N ₃ O ₂
307860	CF3	H	COPh	C ₃₂ H ₃₂ F ₃ N ₃ O ₃
307861	CF3	H	2,4-(Cl)2-PhCH2	C ₃₂ H ₃₂ Cl ₂ F ₃ N ₃ O ₂
307862	CF3	H	2,3-(F)2-PhCH2	C ₃₂ H ₃₂ F ₃ N ₃ O ₂
307863	CF3	H	9-fluorenyl-CH2	C ₃₉ H ₃₈ F ₃ N ₃ O ₂
307864	CF3	(S)-Me	2,4-(Cl)2-PhCH2	C ₃₃ H ₃₄ Cl ₂ F ₃ N ₃ O ₂
307865	CF3	(R)-Me	2,4-(Cl)2-PhCH2	C ₃₃ H ₃₄ Cl ₂ F ₃ N ₃ O ₂

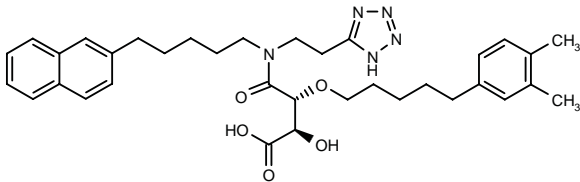
SOURCE – Boehringer Ingelheim.

REFERENCES

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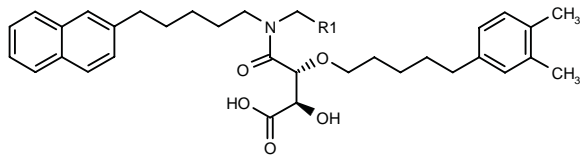
308643

3(*R*)-[5-(3,4-Dimethylphenyl)pentyl]oxy]-2(*R*)-hydroxy-3-[*N*-[5-(2-naphthyl)pentyl]-*N*-[2-(1*H*-tetrazol-5-yl)ethyl]-carbamoyl]propionic acid



C35 H45 N5 O5; Mol wt: 615.7705

ACTION – Squalene synthase inhibitor (IC₅₀ = 0.071 nM against enzyme from HepG2 cells) found to inhibit the biosynthesis of cholesterol in rat hepatic cells (IC₅₀ = 0.81 nM). Potentially useful for the treatment of hypercholesterolemia, hyperlipidemia and arteriosclerosis. Other exemplified succinamide derivatives are:



Compound	R1	Formula
308644	2-oxo-2,3-dihydro-1,3,4-oxadiazol-5-yl	C ₃₆ H ₄₃ N ₃ O ₇
308645	CH2CONHSO2Me	C ₃₆ H ₄₈ N ₂ O ₈ S

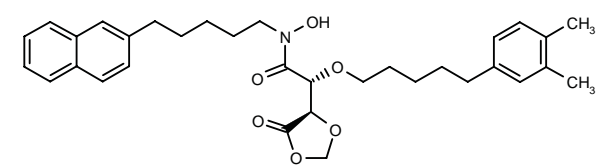
SOURCE – Daiichi Pharmaceutical.

REFERENCES

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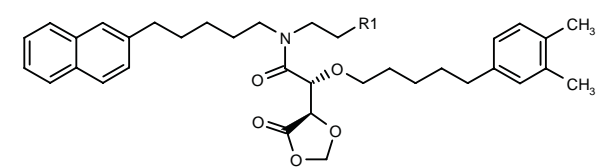
308646

2(*R*)-[5-(3,4-Dimethylphenyl)pentyl]oxy]-*N*-[5-(2-naphthyl)pentyl]-2-[5-oxo-1,3-dioxolan-4(*R*)-yl]acetohydroxamic acid



C33 H41 N O6; Mol wt: 547.6879

ACTION – Squalene synthase inhibitor (IC₅₀ = 1.3 nM against enzyme from HepG2 cells) prevent to inhibit the biosynthesis of cholesterol in rat hepatic cells (C₅₀ = 0.045 μM). Potentially useful for the treatment of hypercholesterolemia, hyperlipidemia and arteriosclerosis. Other exemplified dioxolane derivatives are:



Compound	R1	Formula
308647	CONHSO2Me	C ₃₇ H ₄₈ N ₂ O ₈ S
308648	5-tetrazolyl	C ₃₆ H ₄₅ N ₅ O ₅

SOURCE – Daiichi Pharmaceutical.

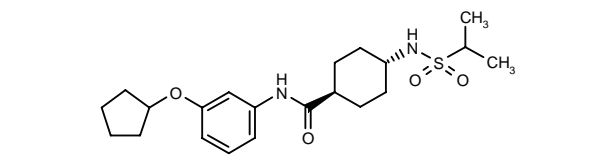
REFERENCES

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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

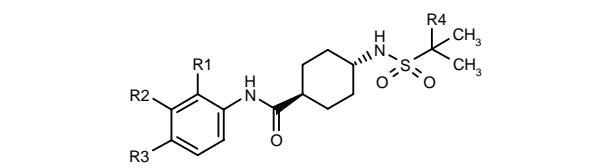
305690

trans-*N*-[3-(Cyclopentyloxy)phenyl]-4-(isopropylsulfonamido)cyclohexanecarboxamide



C21 H32 N2 O4 S; Mol wt: 408.5598

ACTION – Antiobesity agent, a selective neuropeptide Y (NPY) Y₅ receptor antagonist, as demonstrated by strong inhibition of [¹²⁵I]-PYY binding to human Y₅ receptors expressed in CHO cells (IC₅₀ = 0.11 nM), while having no effect on Y₁ and Y₂ receptors (IC₅₀ = 100 μM or greater). Antagonist activity was demonstrated in functional assays by inhibition of forskolin-stimulated cAMP production in CHO cells expressing the human Y₅ receptor (IC₅₀ = 1.6 nM). Other compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
305691	H	H	1-pyrrolidinyl	Me	C ₂₁ H ₃₃ N ₅ O ₃ S
305692	H	H	1-pyrrolyl	Me	C ₂₁ H ₂₉ N ₅ O ₃ S
305693	H	H	CF3	Me	C ₁₈ H ₂₅ F ₃ N ₂ O ₃ S
305694	H	H	OCF3	Me	C ₁₈ H ₂₅ F ₃ N ₂ O ₄ S
305695	H	Cl	Cl	Me	C ₁₇ H ₂₄ Cl ₂ N ₂ O ₃ S
305696	H	H	cis-3,5-(Me)2-1-Pip	Me	C ₂₄ H ₃₉ N ₅ O ₃ S
305697	Me	H	cis-2,6-(Me)2-4-morpholinyl	H	C ₂₃ H ₃₇ N ₅ O ₄ S
305699	H	H	i-PrNHCO	Me	C ₂₁ H ₃₃ N ₅ O ₄ S

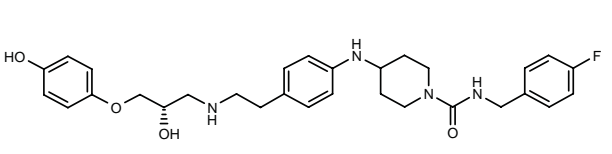
SOURCE – Shionogi.

REFERENCES

1. Kawanishi, Y. et al. (Shionogi & Co. Ltd.) *NPYY5 antagonists.* WO 0137826.

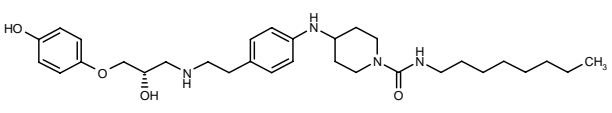
307677

N-(4-Fluorobenzyl)-4-[4-[2-[2(*S*)-hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl]phenylamino]piperidine-1-carboxamide



C30 H37 F N4 O4; Mol wt: 536.6443

ACTION – Potent human β₃-adrenoceptor agonist (EC₅₀ = 8 nM; intrinsic activity = 150%, isoproterenol = 100%) with high selectivity over β₁-adrenoceptors (EC₅₀ = 610 nM) and no activity at β₂-adrenoceptors. *In vivo*, compound increased thermogenesis (11% at 10 mg/kg i.p.) in a transgenic mouse model. Potentially useful for the treatment of obesity. Another related compound is:



307676: C31 H48 N4 O4

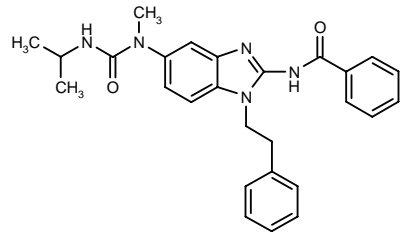
SOURCE – Wyeth-Ayerst.

REFERENCES

1. Solvibile, W.R. et al. *Potent, selective agonists of the human β_3 -adrenergic receptor*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 35.

307680

N-[5-(3-Isopropyl-1-methylureido)-1-(2-phenylethyl)-1H-benzimidazol-2-yl]benzamide



C27 H29 N5 O2; Mol wt: 455.5591

ACTION – Neuropeptide Y (NPY) Y_5 antagonist, a urea derivative with good affinity for the human Y_5 receptor (IC_{50} = 81 nM) and good stability and cell permeability properties *in vitro*. Furthermore, high brain levels and a favorable brain/plasma ratio were found in rats at a dose of 25 mg/kg p.o. Potentially useful for the treatment of obesity.

SOURCE – GlaxoSmithKline.

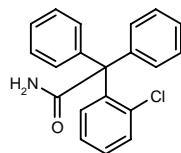
REFERENCES

1. Akwabi-Ameyaw, A. et al. *Synthesis and SAR of substituted 5-acylamino benzimidazoles as potent neuropeptide Y Y_5 antagonists*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 33.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

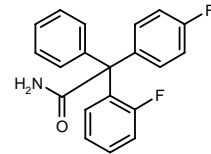
308634

2-(2-Chlorophenyl)-2,2-diphenylacetamide



C20 H16 Cl N O; Mol wt: 321.8054

ACTION – An inhibitor of Ca^{2+} -activated potassium (Gardos) channels with an IC_{50} of 10 nM against the erythrocyte Gardos channel, and high selectivity over other potassium channels. Potentially useful for the treatment of sickle cell disease. Other exemplified triphenyl-substituted carboxamides are:



Compound	Isomer	Formula
308635	racemic	$C_{20}H_{15}F_2NO$
308636	S	$C_{20}H_{15}F_2NO$
308637	R	$C_{20}H_{15}F_2NO$

SOURCE – ICAgen.

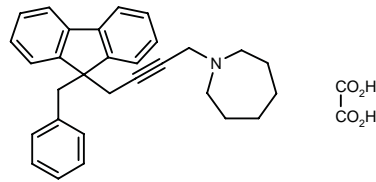
REFERENCES

1. McNaughton-Smith, G.A. et al. (ICAgen, Inc.) *Gardos channel antagonists*. US 6288122.

UCL-1608

308014

1-[4-(9-Benzyl-9H-fluoren-9-yl)-2-butynyl]perhydroazepine oxalate



C30 H31 N . C2 H2 O4; Mol wt: 495.6157

ACTION – Intermediate-conductance Ca^{2+} -activated potassium (IK_{Ca}) channel blocker, an analogue of cetiedil with improved potency for inhibition of IK_{Ca} -mediated permeability in red blood cells (IC_{50} = 1.5 μ M and 25 μ M, respectively). Potentially useful for the treatment of sickle cell disease.

SOURCE – University College London, London (GB).

REFERENCES

1. Roxburgh, C.J. et al. *Synthesis and structure-activity relationships of cetiedil analogues as blockers of the Ca^{2+} -activated K^+ permeability of erythrocytes*. J Med Chem 2001, 44(20): 3244.

DIAGNOSTIC AGENTS

FERUCARBOTRAN*

USAN

214464

Superparamagnetic iron oxide (magnetic- Fe_3O_4 /mag-hemite- γ - Fe_2O_3) contrast agent consisting of carboxydextran-coated iron oxide particles with a hydrodynamic particle size of approximately 60 nm

Magnetites
SHU-555A+
ZK-132281

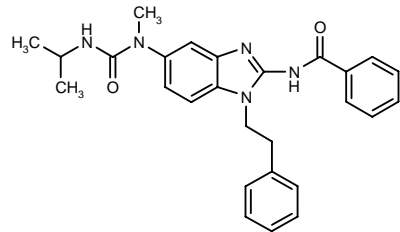
SOURCE – Wyeth-Ayerst.

REFERENCES

1. Solvibile, W.R. et al. *Potent, selective agonists of the human β_3 -adrenergic receptor*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 35.

307680

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SOURCE – GlaxoSmithKline.

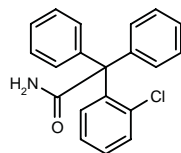
REFERENCES

1. Akwabi-Ameyaw, A. et al. *Synthesis and SAR of substituted 5-acylamino benzimidazoles as potent neuropeptide Y Y_5 antagonists*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 33.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

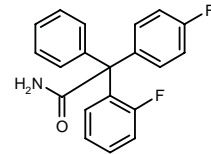
308634

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308637	R	$C_{20}H_{15}F_2NO$

SOURCE – ICAgen.

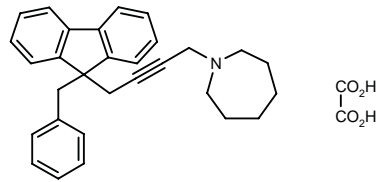
REFERENCES

1. McNaughton-Smith, G.A. et al. (ICAgen, Inc.) *Gardos channel antagonists*. US 6288122.

UCL-1608

308014

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ACTION – Intermediate-conductance Ca^{2+} -activated potassium (IK_{Ca}) channel blocker, an analogue of cetiedil with improved potency for inhibition of IK_{Ca} -mediated permeability in red blood cells (IC_{50} = 1.5 μ M and 25 μ M, respectively). Potentially useful for the treatment of sickle cell disease.

SOURCE – University College London, London (GB).

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DIAGNOSTIC AGENTS

FERUCARBOTRAN*

USAN

214464

Superparamagnetic iron oxide (magnetic- Fe_3O_4 /mag-hemite- γ - Fe_2O_3) contrast agent consisting of carboxydextran-coated iron oxide particles with a hydrodynamic particle size of approximately 60 nm

Magnetites
SHU-555A+
ZK-132281

ACTION – Liver-specific superparamagnetic iron oxide contrast agent for magnetic resonance imaging.

INDICATION – Detection and characterization of focal liver lesions.

PRESENTATION – Solution for injection, 28 mg/ml iron in the form of ferucarbotran, which consists of superparamagnetic iron oxide nanoparticles coated with carboxy-dextran in an approximate ratio of 1:1.1 (w/w); available as vials (2.0 ml) filled with 1.6 ml and prefilled syringes (2.25 ml) filled with 0.9, 1.11 and 1.4 ml.

PROPRIETARY NAME – Resovist (SE).

SOURCES – Schering AG; developed in collaboration with Meito Sangyo.

REFERENCES

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2. Blakeborough, A. et al. *Superparamagnetic iron oxide-enhanced MRI of focal liver lesions: Comparison with fat saturated T2WSE and dynamic contrast-enhanced turboFLASH images*. Br J Radiol 1996, 69(Suppl.): 26.
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6. Kato, N. et al. *General pharmacological study with SH U 555 A, a liver specific MRI contrast agent (I) - Effect on respiratory and cardiovascular system in rats and guinea pigs*. Jpn Pharmacol Ther 1998, 26(10): 149.
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13. Shamsi, K. et al. *Superparamagnetic iron oxide particles (SH U 555 A): Evaluation of efficacy in three doses for hepatic MR imaging*. Radiology 1998, 206(2): 365.
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15. *E.C. clears Resovist via mutual recognition procedure*. DailyDrugNews.com (Daily Essentials) 2001, Aug 23.
16. *Liver-specific MRI contrast agent launched in Sweden*. DailyDrugNews.com (Daily Essentials) 2001, Sept 10.
17. *Schering AG makes good start to 2001*. DailyDrugNews.com (Daily Essentials) 2001, May 4.
18. *Schering AG's liver-specific contrast agent approved in Sweden*. DailyDrugNews.com (Daily Essentials) 2001, March 30.
19. *Schering AG: Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1999, May 19.

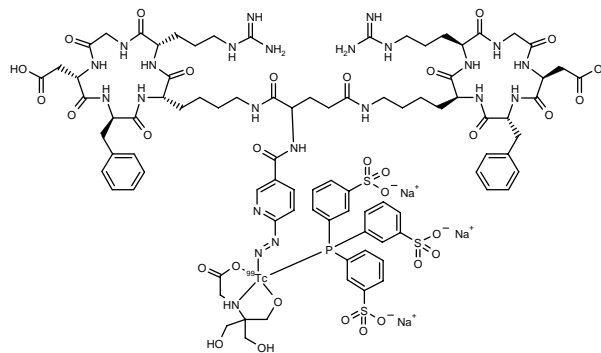
*Drug Data Rep 1995, 017(01): 0106.

[99Tc]-RP-593

301807

Trisodium dihydrogen [[5,5'-[N-[[6-(diazanyl-κN²)-3-pyridinyl]carbonyl]-L-glutamoyl]bis[cyclo(L-arginylglycyl-L-α-aspartyl-D-phenylalanyl-L-lysylato)]](3-)][N-2-(hydroxy-κO)-1-[(hydroxy-κO)methyl]-1-(hydroxymethyl)ethyl]-glycinato(2-)-κN,κO][[3,3',3''-(phosphinidyne-κP)tris[benzenesulfonato]](3-)]technetate(5-)-99Tc

^{99m}Tc-c(RGDfK*)2HYNIC



C89 H112 N23 Na3 O31 P S3 Tc; Mol wt: 2295.1360

ACTION – ^{99m}Tc-Labeled nonpeptide integrin α_vβ₃ and α_vβ₅ antagonist (IC₅₀ = 0.9 and 6 nM, respectively) with high selectivity over α_vβ₁ and gpIIb/IIIa receptors (IC₅₀ > 10 μM). It is able to detect spontaneous tumors in mice and dogs. In biodistribution experiments performed in mice bearing human ovarian carcinoma OVCAR-3 or dogs with spontaneous mammary carcinoma, compound exhibited good tumor uptake and retention for at least 24 h. Potentially useful as a diagnostic agent for detecting solid tumors.

SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

REFERENCES

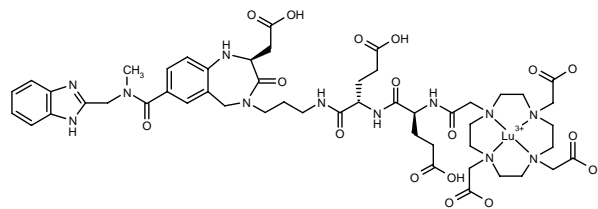
1. Rajopadhye, M. et al. (DuPont Pharmaceuticals Co.) *Pharmaceuticals for the imaging of angiogenic disorders*. EP 1068224, WO 9958162.
2. Barrett, J.A. et al. *RP593, a ^{99m}Tc-labeled α_vβ₃/α_vβ₅ antagonist, rapidly detects spontaneous tumors in mice and dogs*. J Nucl Med 2000, 41(5, Suppl.): Abst 132.
3. Barrett, J.A. et al. *RP593, a ^{99m}Tc-labeled Avb3 antagonist, rapidly detects spontaneous tumors in mice and dogs*. Proc Amer Assoc Cancer Res 2001, 42: Abst 2194.
4. Janssen, M.L.H. et al. *¹¹¹In And ^{99m}Tc labeled peptides against the α_vβ₃ integrin: A new target for radionuclide peptide targeting of tumors*. J Nucl Med 2000, 41(5, Suppl.): Abst 129.
5. Liu, S. et al. *Tc-99m-Labeling of a hydrazinonicotinamide-conjugated vitronectin receptor antagonist useful for imaging tumors*. Bioconjugate Chem 2001, 12(4): 624.

RP-698^{1,2}

307703

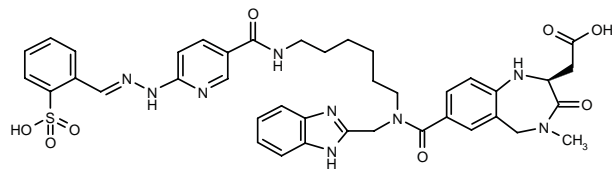
[N-[2-[4,7,10-Tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl]-L-glutamyl-N¹-[3-[7-[N-(1*H*-benzimidazol-2-ylmethyl)-N-methylcarbamoyl]-2(*S*)-(carboxymethyl)-3-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-4-yl]propyl]-L-α-glutaminato(3-)]lutetium-177Lu

SU-058 (uncomplexed)

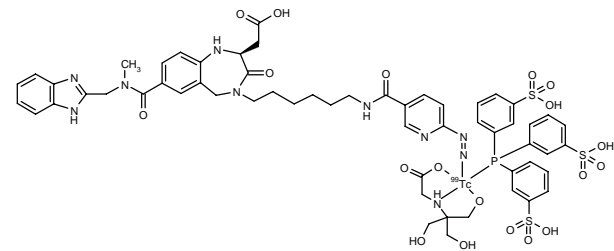


C50 H65 Lu N12 O17; Mol wt: 1281.1000

ACTION – Nonpeptide vitronectin receptor ($\alpha_v\beta_3$ integrin) antagonist for imaging tumors. The unlabeled compound (SU-058) inhibited binding of biotinylated vitronectin with an IC_{50} of 0.0035 μ M versus a value of 3.5 μ M against iodinated fibrinogen binding. When given to transgenic *c-neu* mice, the ¹⁷⁷Lu complex showed good uptake in mammary tumors, producing clear tumor images, and was primarily excreted in urine with low bile activity. Another related complex and its free form are:



SU-055² [308616]: C40 H43 N9 O8 S



RP-627² [308617]: C39 H47 N10 O10 Tc . C18 H15 O9 P S3

SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

REFERENCES

1. Cheesman, E.H. et al. (DuPont Pharmaceuticals Co.) *Vitronectin receptor antagonist pharmaceuticals*. EP 1140864, WO 0035887.

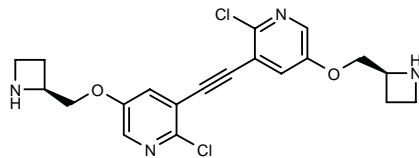
2. Cheesman, E.H. et al. *Nonpeptide vitronectin antagonists labeled with Tc99m for imaging tumors*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MED1 77.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

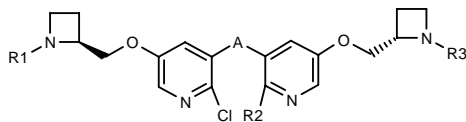
308664

3,3'-(Ethynylene-1,2-diyl)bis[5-[azetidin-2(*S*)-ylmethoxy]-2-chloropyridine]

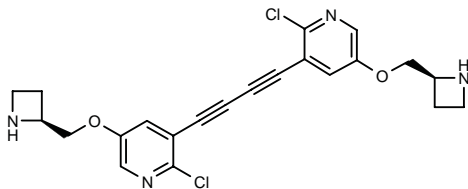


C20 H20 Cl2 N4 O2; Mol wt: 419.3100

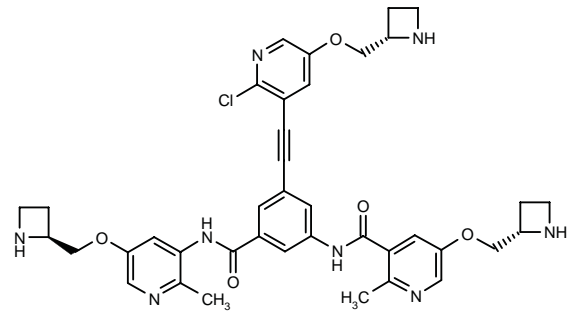
ACTION – Analgesic agent that acts as a modulator of nicotinic acetylcholine receptors, binding to the receptors in a multivalent mode. Other exemplified compounds are:



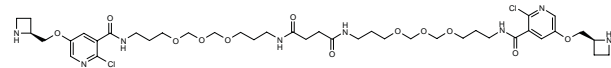
Compound	R1	R2	R3	A	Formula
308665	H	Cl	H	(E)-CH=CH-	C ₂₀ H ₂₂ Cl ₂ N ₄ O ₂
308666	H	Cl	H	(Z)-CH=CH-	C ₂₀ H ₂₂ Cl ₂ N ₄ O ₂
308667	H	Cl	H	-(CH ₂) ₂ -	C ₂₀ H ₂₄ Cl ₂ N ₄ O ₂
308673	H	Cl	H	-(CH ₂) ₄ -	C ₂₂ H ₂₈ Cl ₂ N ₄ O ₂
308674	H	Cl	H	-ethynylene-1,4-Ph-ethynylene-	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂
308676	H	Cl	H	-CH ₂ CH ₂ -1,4-Ph-CH ₂ CH ₂ -	C ₂₈ H ₃₂ Cl ₂ N ₄ O ₂
308678	H	Cl	H	-NHCOCH ₂ -1,4-Ph-CH ₂ CONH-	C ₂₈ H ₃₀ Cl ₂ N ₆ O ₄
308679	H	Cl	H	-CONHCH ₂ -1,4-Ph-CH ₂ NHCO-	C ₂₈ H ₃₀ Cl ₂ N ₆ O ₄
308680	H	Me	H	-NHCOCH ₂ NHCO-	C ₂₂ H ₂₇ ClN ₆ O ₄
308684	Me	Cl	Me	-(CH ₂) ₂ -	C ₂₂ H ₂₈ Cl ₂ N ₄ O ₂



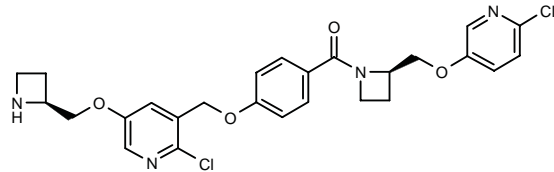
308668: C22 H20 Cl2 N4 O2



308681: C39 H41 Cl N8 O5



308682: C40 H60 Cl2 N8 O12



308683: C26 H26 Cl2 N4 O4

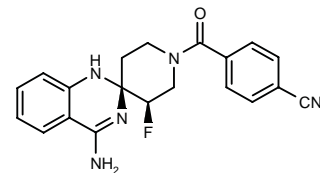
SOURCE – Advanced Medicine.

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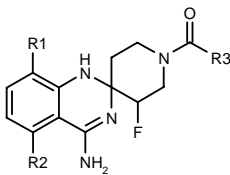
308823

cis-4-(4'-Amino-3-fluorospiro[piperidine-4,2'(1'*H*)-quinazolin]-1-ylcarbonyl)benzonitrile



C20 H18 F N5 O; Mol wt: 363.3942

ACTION – An inhibitor of nitric oxide synthase, particularly the inducible isoform (iNOS), expected to be useful for the treatment of inflammation and pain (including chronic, acute and neuropathic pain). Other specifically claimed spiro compounds are:



Compound	R1	R2	R3	Isomer	Formula
308837	H	H	4-Me-Ph	trans	C ₂₀ H ₂₁ FN ₄ O
308838	H	F	4-Cl-Ph	cis	C ₁₉ H ₁₇ ClF ₂ N ₄ O
308839	H	F	4-Me-Ph	cis	C ₂₀ H ₂₀ F ₂ N ₄ O
308843	F	F	6-CN-3-Pyr	(-)-2'S,3S	C ₁₉ H ₁₅ F ₃ N ₆ O
308844	F	F	2-furyl	cis	C ₁₇ H ₁₅ F ₃ N ₄ O ₂
308846	F	F	4-CN-Ph	(+)-2'S,3R	C ₂₀ H ₁₆ F ₃ N ₅ O
308847	F	F	5-CN-2-Pyr	trans	C ₁₉ H ₁₅ F ₃ N ₆ O

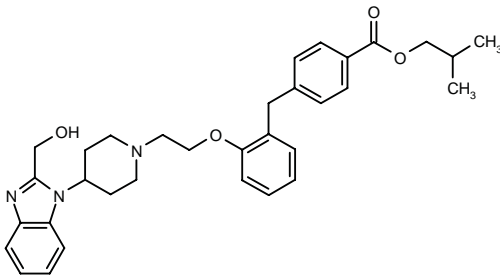
SOURCE – AstraZeneca.

REFERENCES

1. Walpole, C. and Yang, H. (AstraZeneca AB) *Novel cpds.* WO 0158867.

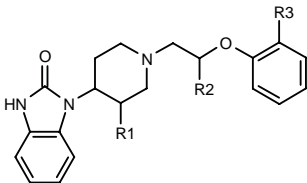
308956

4-[2-[2-[4-[2-(Hydroxymethyl)-1-*H*-benzimidazol-1-yl]piperidin-1-yl]ethoxy]benzyl]benzoic acid isobutyl ester

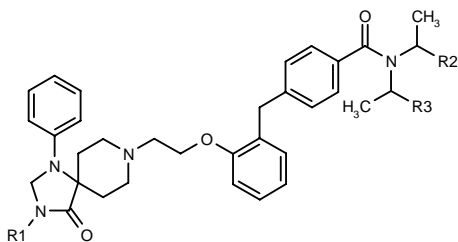


C33 H39 N3 O4; Mol wt: 541.6881

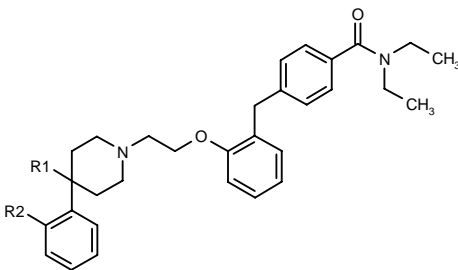
ACTION – Delta opioid receptor agonist found to inhibit the binding of [³H]-naltrindole in rat brain preparations with a K_i of 73 nM. Potentially useful for the treatment of CNS disorders including schizophrenia, depression, stroke, epilepsy, Alzheimer’s disease and Parkinson’s disease, as well as peripheral nervous system disorders such as pain. Other exemplified phenoxyalkylamine derivatives are:



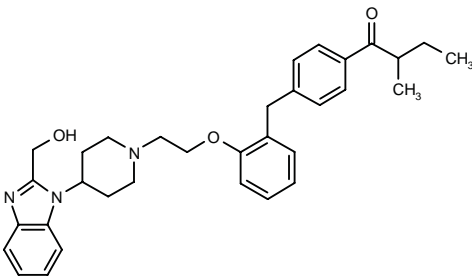
Compound	R1	R2	R3	Formula
308961	H	H	4-(1-pyrrolidinyl-CO)-PhCH2	C ₃₂ H ₃₆ N ₄ O ₃
308962	H	Me	4-[N(Et)2CO]-PhCH2	C ₃₃ H ₄₀ N ₄ O ₃
308964	H	H	4-[N(Et)2CO]-PhCH2CH2	C ₃₃ H ₄₀ N ₄ O ₃
308966	H	H	4-[N(Et)2CO]-Ph	C ₃₁ H ₃₆ N ₄ O ₃
308968	Me	H	4-[N(Et)2CO]-PhCH2	C ₃₃ H ₄₀ N ₄ O ₃
308969	H	H	trans-4-[N(Et)2CO]-cyclohexyl-CH2	C ₃₂ H ₄₄ N ₄ O ₃



Compound	R1	R2=R3	Formula
308963	H	Me	C ₃₈ H ₄₄ N ₄ O ₃
308965	Me	H	C ₃₄ H ₄₂ N ₄ O ₃



Compound	R1	R2	Formula
308967	Ac	H	C ₃₃ H ₄₀ N ₂ O ₃
308971	-CH2N(CH2Ph)CO-		C ₄₀ H ₄₆ N ₃ O ₃



308970: C33 H39 N3 O3

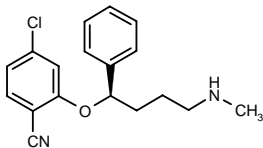
SOURCE – Meiji Seika.

REFERENCES

1. Tsushima, M. et al. (Meiji Seika Kaisha, Ltd.) *Phenoxyalkylamine derivs. useful as opioid delta receptor agonists.* WO 0160796.

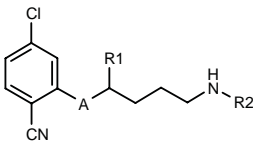
309566

4-Chloro-2-[4-(methylamino)-1(*R*)-phenylbutoxy]-benzonitrile



C18 H19 Cl N2 O; Mol wt: 314.8141

ACTION – An inhibitor of inducible nitric oxide synthase (iNOS) with potential in the treatment or prevention of inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis and osteoarthritis, and pain. Other specifically claimed compounds from this series of phenylheteroalkylamine derivatives include the following:



Compound	R1	R2	A	Formula
309567	(R)-Ph	5-imidazolyl-CH2CH2	O	C ₂₂ H ₂₃ ClN ₄ O
309568	(R)-Ph	(R)-CH(Me)CH2OH	O	C ₂₀ H ₂₃ ClN ₂ O ₂
309569	(R)-Ph	H	NH	C ₁₇ H ₁₈ ClN ₃
309570	3-thienyl	Me	O	C ₁₆ H ₁₇ ClN ₂ OS
309571	2-Pyr	Et	O	C ₁₈ H ₂₀ ClN ₃ O
309572	2-oxo-1,2-dihydro-3-Pyr	H	O	C ₁₆ H ₁₆ ClN ₃ O ₂
309573	1-Me-1,2,4-triazol-5-yl	H	O	C ₁₄ H ₁₆ ClN ₅ O

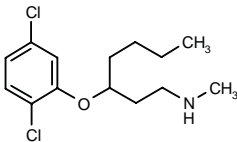
SOURCE – AstraZeneca.

REFERENCES

1. Birkinshaw, T. et al. (AstraZeneca AB) *Novel phenylheteroalkylamine derivs.* WO 0162713.

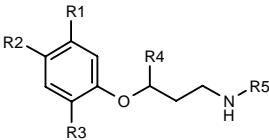
309574

N-[3-(2,5-Dichlorophenoxy)heptyl]-N-methylamine



C14 H21 Cl2 N O; Mol wt: 290.2319

ACTION – An inhibitor of inducible nitric oxide synthase (iNOS) with potential in the treatment or prevention of inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis and osteoarthritis, and pain. Other specifically claimed compounds from this series of phenylheteroalkylamine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
309575	Cl	H	Cl	i-Bu	Me	C ₁₄ H ₂₁ Cl ₂ NO
309577	Cl	H	CN	Pr	Me	C ₁₄ H ₁₉ ClN ₂ O
309578	Cl	H	NO2	Bu	Me	C ₁₄ H ₂₁ ClN ₂ O ₃
309579	CF3	H	Cl	Bu	Me	C ₁₅ H ₂₁ ClF ₃ NO
309581	Cl	H	CN	CF3	Me	C ₁₂ H ₁₂ ClF ₃ N ₂ O
309582	Cl	F	CN	CF3	Me	C ₁₂ H ₁₁ ClF ₄ N ₂ O
309583	Cl	F	CN	Et	CH2CH2OMe	C ₁₅ H ₂₀ ClFN ₂ O ₂
309584	Cl	H	CN	(R)-CH2OMe	H	C ₁₂ H ₁₅ ClN ₂ O ₂

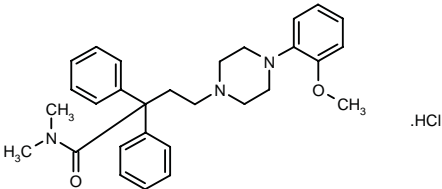
SOURCE – AstraZeneca.

REFERENCES

1. Cheshire, D. et al. (AstraZeneca AB) *Novel phenylheteroalkylamine derivs.* WO 0162714.

310013

4-[4-(2-Methoxyphenyl)piperazin-1-yl]-N,N-dimethyl-2,2-diphenylbutyramide hydrochloride



C29 H35 N3 O2 . HCl; Mol wt: 494.0754

ACTION – Potent and selective mu opioid receptor agonist with high affinity for mu over delta and kappa opioid receptors (IC₅₀ = 0.28, 180 and 2000 nM, respectively) and functional agonist activity in isolated guinea pig ileum, where it was 12-fold more potent than DAMGO for inhibition of electrically stimulated muscle contractions. Potentially useful as an analgesic agent.

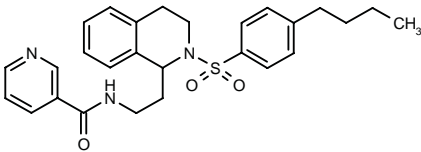
SOURCE – SSP.

REFERENCES

1. Komoto, T. et al. *New μ-opioid receptor agonists with piperazine moiety.* Chem Pharm Bull 2001, 49(10): 1314.

310418

N-[2-[2-(4-Butylphenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]ethyl]pyridine-3-carboxamide



C27 H31 N3 O3 S; Mol wt: 477.6259

ACTION – Potent and selective delta opioid receptor ligand (IC₅₀ = 172, 1680 and > 10,000 nM for opioid delta, kappa and mu receptors, respectively) with strong analgesic activity comparable to morphine in the mouse formalin paw test.

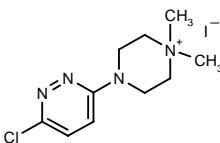
SOURCES – AstraZeneca; Organon.

REFERENCES

1. Barn, D.R. et al. *Parallel synthesis and biological activity of a new class of high affinity and selective δ-opioid ligand.* Bioorg Med Chem 2001, 9(10): 2609.

310546

4-(6-Chloropyridazin-3-yl)-1,1-dimethylpiperazin-1-ium iodide



C10 H16 Cl I N4; Mol wt: 354.6174

ACTION – High-affinity ligand for neuronal $\alpha 4\beta 2$ nicotinic acetylcholine receptors ($K_i = 4.5$ nM) proven to induce mecamylamine-dependent analgesia in the hot-plate test in mice with a minimal analgesic dose of 0.1 $\mu\text{g/kg}$ i.c.v. Potentially useful as an analgesic agent and for the treatment of neurodegenerative diseases.

SOURCES – Università di Ferrara, Ferrara (IT); Università degli Studi di Firenze, Firenze (IT).

REFERENCES

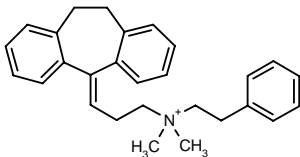
1. Romanelli, M.N. et al. *Structure-affinity relationships of a unique nicotinic ligand: N1-dimethyl-N4-phenylpiperazinium iodide (DMPP)*. J Med Chem 2001, 44(23): 3946.

ANESTHETIC DRUGS

N-PHENYLETHYL AMITRIPTYLINE

309682

3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-N-(2-phenylethyl)-1-propanaminium



C28 H32 N; Mol wt: 382.5678

ACTION – Long-acting local anesthetic, a quaternary ammonium derivative of amitriptyline with at least 8-fold superior Na^+ channel-blocking activity *in vitro*. Compound at 2.5 mM completely blocked rat sciatic nerve with a time to full recovery from sciatic nerve block of 30.3 h; the duration of complete nociceptive block was 3.2-fold longer than for amitriptyline and time to complete recovery of nociception was 11.7-fold longer than for bupivacaine. Selected as a candidate for further preclinical investigation.

SOURCE – Brigham & Women’s Hospital, Boston, MA (US).

REFERENCES

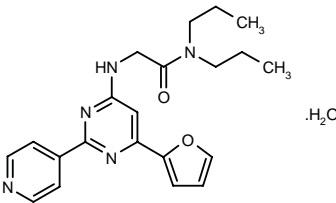
1. Sudoh, Y. et al. *N-Phenylethyl amitriptyline acts as a long acting local anesthetic in rat*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-988.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

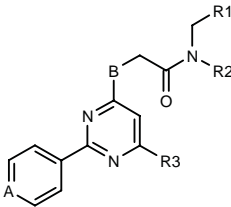
309251

2-[6-(2-Furyl)-2-(4-pyridyl)pyrimidin-4-ylamino]-N,N-dipropylacetamide hydrate



C21 H25 N5 O2 . H2O; Mol wt: 397.4763

ACTION – A selective benzodiazepine $\omega 3$ receptor (BZ $\omega 3$) ligand with an IC_{50} of 2.9 nM when tested *in vitro* against BZ $\omega 3$ -containing membrane preparations, and > 300-fold selectivity over the $\omega 1$ and $\omega 2$ receptor subtypes. Potentially useful for the treatment of anxiety, CNS disorders including depression and epilepsy, circulatory disorders including angina pectoris and hypertension, immune neuropathies such as multiple sclerosis, and immune inflammatory diseases. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	B	Formula
309252	H	4-Cl-Ph	3-Pyr	CH	NH	C ₂₄ H ₂₀ ClN ₅ O
309253	Et	Pr	2-furyl	CH	NH	C ₂₂ H ₂₆ N ₄ O ₂
309255	H	Ph	2-furyl	CH	O	C ₂₃ H ₁₉ N ₃ O ₃
309257	Et	Pr	2-furyl	CH	O	C ₂₂ H ₂₅ N ₃ O ₃
309258	H	Ph	2-furyl	N	O	C ₂₂ H ₁₈ N ₄ O ₃

SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Murata, A. et al. (Dainippon Pharmaceutical Co., Ltd.) *6-Heteroarylpyrimidine derivs. and medicinal compsns. containing them*. JP 2001199982.

ACTION – High-affinity ligand for neuronal $\alpha 4\beta 2$ nicotinic acetylcholine receptors ($K_i = 4.5$ nM) proven to induce mecamylamine-dependent analgesia in the hot-plate test in mice with a minimal analgesic dose of 0.1 $\mu\text{g/kg}$ i.c.v. Potentially useful as an analgesic agent and for the treatment of neurodegenerative diseases.

SOURCES – Università di Ferrara, Ferrara (IT); Università degli Studi di Firenze, Firenze (IT).

REFERENCES

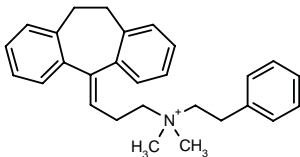
1. Romanelli, M.N. et al. *Structure-affinity relationships of a unique nicotinic ligand: N1-dimethyl-N4-phenylpiperazinium iodide (DMPP)*. J Med Chem 2001, 44(23): 3946.

ANESTHETIC DRUGS

N-PHENYLETHYL AMITRIPTYLINE

309682

3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-N-(2-phenylethyl)-1-propanaminium



C28 H32 N; Mol wt: 382.5678

ACTION – Long-acting local anesthetic, a quaternary ammonium derivative of amitriptyline with at least 8-fold superior Na^+ channel-blocking activity *in vitro*. Compound at 2.5 mM completely blocked rat sciatic nerve with a time to full recovery from sciatic nerve block of 30.3 h; the duration of complete nociceptive block was 3.2-fold longer than for amitriptyline and time to complete recovery of nociception was 11.7-fold longer than for bupivacaine. Selected as a candidate for further preclinical investigation.

SOURCE – Brigham & Women’s Hospital, Boston, MA (US).

REFERENCES

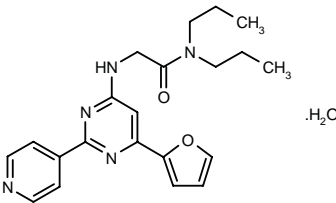
1. Sudoh, Y. et al. *N-Phenylethyl amitriptyline acts as a long acting local anesthetic in rat*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-988.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

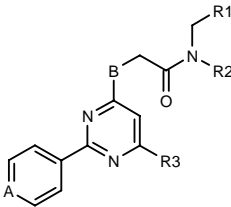
309251

2-[6-(2-Furyl)-2-(4-pyridyl)pyrimidin-4-ylamino]-N,N-dipropylacetamide hydrate



C21 H25 N5 O2 . H2O; Mol wt: 397.4763

ACTION – A selective benzodiazepine $\omega 3$ receptor (BZ $\omega 3$) ligand with an IC_{50} of 2.9 nM when tested *in vitro* against BZ $\omega 3$ -containing membrane preparations, and > 300-fold selectivity over the $\omega 1$ and $\omega 2$ receptor subtypes. Potentially useful for the treatment of anxiety, CNS disorders including depression and epilepsy, circulatory disorders including angina pectoris and hypertension, immune neuropathies such as multiple sclerosis, and immune inflammatory diseases. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	B	Formula
309252	H	4-Cl-Ph	3-Pyr	CH	NH	C ₂₄ H ₂₀ ClN ₅ O
309253	Et	Pr	2-furyl	CH	NH	C ₂₂ H ₂₆ N ₄ O ₂
309255	H	Ph	2-furyl	CH	O	C ₂₃ H ₁₉ N ₃ O ₃
309257	Et	Pr	2-furyl	CH	O	C ₂₂ H ₂₅ N ₃ O ₃
309258	H	Ph	2-furyl	N	O	C ₂₂ H ₁₈ N ₄ O ₃

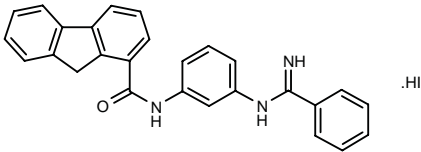
SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Murata, A. et al. (Dainippon Pharmaceutical Co., Ltd.) *6-Heteroarylpyrimidine derivs. and medicinal compsns. containing them*. JP 2001199982.

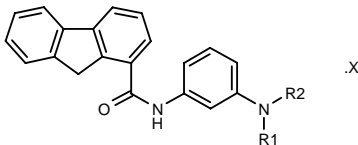
309658

N-[3-(1-Imino-1-phenylmethylamino)phenyl]-9*H*-fluorene-1-carboxamide hydroiodide



C27 H21 N3 O . HI; Mol wt: 531.3908

ACTION – 5-HT_{2C} antagonist, particularly active against the 5-HT_{2C} receptor subtype, proven to inhibit the binding of [³H]-mesulergine in rat prefrontal cortex preparations by 100% at 1 μM. Potentially useful for the treatment of CNS disorders including anxiety, depression, obsessive–compulsive neurosis, migraine, anorexia, Alzheimer’s disease, sleep disorders, polyphagia, panic, schizophrenia, withdrawal from drug abuse and spinal trauma–or head injury-related disorders. Other exemplified amide compounds are:



Compound	R1	R2	X	Formula
309660		=C(Ph)NHMe		C ₂₈ H ₂₃ N ₃ O
309662	Me	C(=NH)Ph	HCl	C ₂₈ H ₂₃ N ₃ O.HCl

SOURCE – Fujisawa.

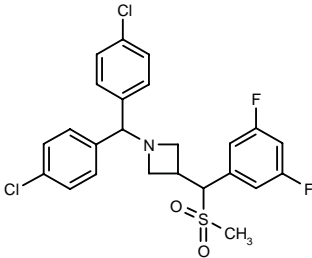
REFERENCES

1. Ito, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel amide cpds.* JP 2001220375.

ANTIPSYCHOTIC DRUGS

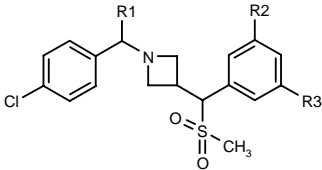
309886

1-[Bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluoro-phenyl)-1-(methylsulfonyl)methyl]azetidine

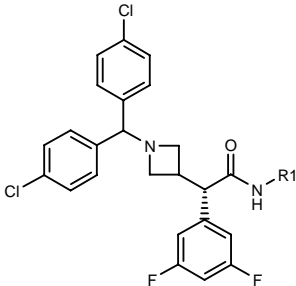


C24 H21 Cl2 F2 N O2 S; Mol wt: 496.4029

ACTION – Cannabinoid CB₁ receptor antagonist potentially useful for the treatment or prevention of schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cognitive disorders, brain trauma, panic attacks, peripheral neuropathy, glaucoma, migraine, Parkinson’s disease, Alzheimer’s disease, Huntington’s chorea, obsessive–compulsive disorder, senile dementia, Tourette’s syndrome, tardive dyskinesia, as well as immune, cardiovascular, endocrine, respiratory, gastro-intestinal and reproductive disorders and cancer. Other specifically claimed compounds from this series of azetidine derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
309887	4-Cl-Ph	H	1-azetidinyI		C ₂₇ H ₂₈ Cl ₂ N ₂ O ₂ S
309889	4-Cl-Ph	CF ₃	CF ₃		C ₂₆ H ₂₁ Cl ₂ F ₆ NO ₂ S
309892	(R)-3-Pyr	F	F	R	C ₂₃ H ₂₁ ClF ₂ N ₂ O ₂ S
309893	(S)-5-pyrimidinyl	F	F	S	C ₂₂ H ₂₀ ClF ₂ N ₃ O ₂ S



Compound	R1	Formula
309890	cyclohexyl	C ₃₀ H ₃₀ Cl ₂ F ₂ N ₂ O
309891	i-Pr	C ₂₇ H ₂₆ Cl ₂ F ₂ N ₂ O

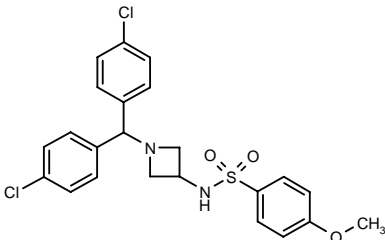
SOURCE – Aventis Pharma.

REFERENCES

1. Achard, D. et al. (Aventis Pharma SA) *Azetidine derivs., preparation thereof and pharmaceutical compsns. containing same.* FR 2805818, WO 0164632.

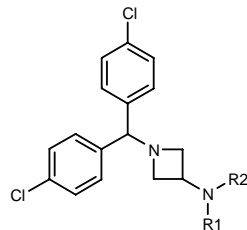
309894

N-[1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl]-4-methoxy-benzenesulfonamide



C23 H22 Cl2 N2 O3 S; Mol wt: 477.4098

ACTION – Cannabinoid CB₁ receptor antagonist potentially useful for the treatment or prevention of schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cognitive disorders, brain trauma, panic attacks, peripheral neuropathy, glaucoma, migraine, Parkinson’s disease, Alzheimer’s disease, Huntington’s chorea, obsessive–compulsive disorder, senile dementia, Tourette’s syndrome, tardive dyskinesia, as well as immune, cardiovascular, endocrine, respiratory, gastro-intestinal and reproductive disorders and cancer. Other specifically claimed compounds from this series of 3-amino-azetidine derivatives include the following:



Compound	R1	R2	Formula
309895	H	3,4-(MeO)2-PhSO2	C ₂₄ H ₂₄ Cl ₂ N ₂ O ₄ S
309896	H	3-CF3-PhSO2	C ₂₃ H ₁₈ Cl ₂ F ₃ N ₂ O ₂ S
309897	H	3-Cl-4-(AcNH)-PhSO2	C ₂₄ H ₂₂ Cl ₃ N ₃ O ₃ S
309898	H	SO2CH2Ph	C ₂₃ H ₂₂ Cl ₂ N ₂ O ₂ S
309899	Me	8-quinolyl-SO2	C ₂₆ H ₂₃ Cl ₂ N ₂ O ₂ S
309901	H	4-Me-PhSO2CH2CO	C ₂₆ H ₂₄ Cl ₂ N ₂ O ₃ S
309906	H	5-(MeSO2)-2-thienyl-CO	C ₂₂ H ₂₀ Cl ₂ N ₂ O ₃ S ₂

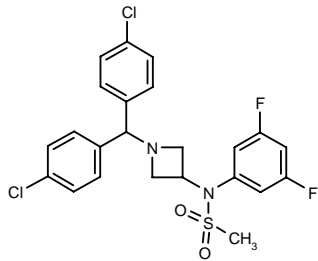
SOURCE – Aventis Pharma.

REFERENCES

1. Achard, D. et al. (Aventis Pharma SA) *Pharmaceutical compsns. containing 3-amino-azetidine derivs., novel derivs. and preparation thereof*. FR 2805810, WO 0164633.

310077

N-[1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl]-*N*-(3,5-difluorophenyl)methanesulfonamide



C23 H20 Cl2 F2 N2 O2 S; Mol wt: 497.3910

ACTION – Cannabinoid CB₁ receptor antagonist, potentially useful for the treatment of CNS disorders including schizophrenia, anxiety, depression, epilepsy, Alzheimer’s disease, Parkinson’s disease, Raynaud’s syndrome, etc. Further applications include immune, cardiovascular, reproductive and endocrine disorders, and diseases related to the respiratory and gastrointestinal systems.

SOURCE – Aventis Pharma.

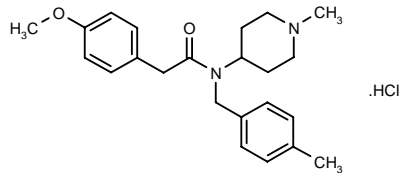
REFERENCES

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AC-90179

310152

2-(4-Methoxyphenyl)-*N*-(4-methylbenzyl)-*N*-(1-methylpiperidin-4-yl)acetamide hydrochloride



C23 H30 N2 O2 . HCl; Mol wt: 402.9629

ACTION – A representative compound from a series of 5-HT modulators that act as inverse agonists at the 5-HT_{2A} receptor subtype. This compound demonstrated *in vivo* activity in the head twitch, locomotor and prepulse inhibition behavioral models following s.c. administration to DOI-treated mice. Potentially useful for the treatment of schizophrenia, migraine and psychosis.

SOURCE – Acadia Pharmaceuticals.

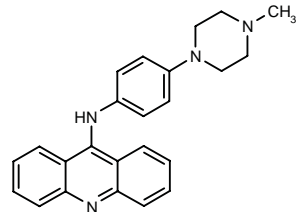
REFERENCES

1. Andersson, C.M. et al. (Acadia Pharmaceuticals, Inc.) *Azacyclic cpds. for use in the treatment of serotonin related diseases*. WO 0166521.
2. Weiner, D.M. et al. *5-Hydroxytryptamine2A receptor inverse agonists as antipsychotics*. J Pharmacol Exp Ther 2001, 299(1): 268.

TREATMENT OF MOOD DISORDERS

309839

N-[4-(4-Methylpiperazin-1-yl)phenyl]acridin-9-amine



C24 H24 N4; Mol wt: 368.4816

ACTION – Selective α_{2C} -adrenoceptor antagonist (K_i = 28 nM) with > 100- and > 50-fold selectivity, respectively, over the α_{2A} - and α_{2B} -adrenoceptor subtypes. In membranes of CHO cells, compound inhibited the epinephrine-stimulated binding of [³⁵S]-GTP γ S to G-proteins with a K_B of 16 nM, thus demonstrating its antagonist activity. In addition, it showed *in vivo* protective activity against stress in the mouse forced swimming test. Potentially useful for the treatment of schizophrenia, depression, stress disorders, Parkinson’s disease and Alzheimer’s disease, while being devoid of cardiovascular side effects.

SOURCES – Juvantia; Orion Corporation.

REFERENCES

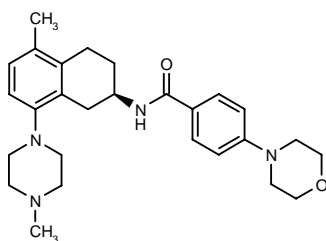
1. Wurster, S. et al. (Juvantia Pharma Ltd.; Orion Corporation) *Derivs. of quinoline as α_2 antagonists*. WO 0164645.

AR-A000002

292815

N-[5-Methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-2(R)-yl]-4-(4-morpholinyl)benzamide

AR-A2XX



C27 H36 N4 O2; Mol wt: 448.6074

ACTION – Potent 5-HT_{1B} receptor antagonist with subnanomolar affinity for 5-HT_{1B} receptors ($K_i = 0.47$ nM against cloned guinea pig receptor) and 10-fold selectivity over 5-HT_{1D} receptors ($K_i = 5.0$ nM); compound exhibited relatively modest affinity for rat 5-HT_{1B} receptors ($K_i = 20$ nM), low affinity for α_1 -adrenoceptors, dopamine D2A, 5-HT_{2A} and 5-HT₇ receptors ($K_i > 330$ nM), and was inactive against 50 other receptors/ion channels tested. In a functional assay, compound exhibited partial agonist activity at the 5-HT_{1B} receptor with a pA₂ of 8.9. Moreover, it blocked the effect of endogenous 5-HT, resulting in enhanced release of [³H]-5-HT in guinea pig brain slices, and in autoradiographic assays the [³H]-labeled compound showed specific binding to the globus pallidus and substantia nigra. *In vivo*, compound given as a single dose or for 3 weeks dose-dependently enhanced 5-HT turnover and 5-HT synthesis in guinea pig brain, and increased extracellular levels of 5-HT and 5-HIAA in guinea pig frontal cortex. Compound exhibited antidepressant effects in three guinea pigs models: a differential reinforcement low rate (DRL) procedure, a response duration differentiation (RDD) schedule and a learned helplessness procedure. Significant anxiolytic activity was seen in the guinea pig separation-induced vocalization test and in a suppressed responding paradigm in pigeons. The anxiolytic effects persisted for at least 7 days after repeated daily treatment, indicating that compound does not induce tolerance. Potentially useful as an anxiolytic and antidepressant.

SOURCE – AstraZeneca.

REFERENCES

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14. Stenfors, C. AR-A000002, *a novel 5-HT_{1B} selective antagonist with antidepressant potential*. Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst S.28.02.

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16. Terelius, Y. et al. AR-A000002, *a high affinity 5-HT_{1B} receptor antagonist: Pharmacokinetic scaling studies*. Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst P.1.078.

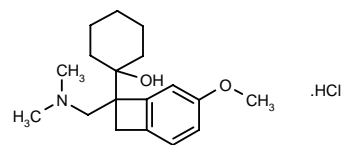
S-33005*

280913

(-)-1-[7-(Dimethylaminomethyl)-4-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]cyclohexanol hydrochloride

S-32647 (racemate)

S-33004 ([+]-enantiomer)



C18 H27 N O2 . HCl; Mol wt: 325.8772

ACTION – High-affinity ligand for the 5-HT transporter ($pK_i = 8.71$ and 8.67 for rat and human transporter, respectively) with lower affinity for the noradrenaline transporter ($pK_i = 6.75$ and 5.82 for rat and human transporter, respectively) and high selectivity over the dopamine transporter and other receptors, enzymes and ion channels. Compound inhibited the reuptake of 5-HT and norepinephrine (NE) into cerebral synaptosomes ($pIC_{50} = 8.6$ and 7.0 , respectively) and prevented *p*-chloroamphetamine-induced depletion of 5-HT from frontal cortex and hippocampus *in vivo* in rats. In freely moving rats, it produced a rapid and substantial elevation in extracellular levels of 5-HT, NE and dopamine in frontal cortex, of 5-HT and NE in hippocampus, and only of 5-HT in nucleus accumbens. In anesthetized rats, it dose-dependently (16 - 2000 μ g/kg i.v.) inhibited the firing rate of raphe neurons, and at higher doses it also blocked the

firing of neurons in the locus ceruleus. Consistent with its binding, electrophysiological and neurochemical profile, the compound showed strong efficacy in behavioral experiments predictive of antidepressant activity including the forced swimming and tail-suspension tests in mice (ID_{50} = 7.4 and 6.8 mg/kg s.c., respectively), marble-burying behavior in mice (ID_{50} = 3.5 mg/kg s.c.) and aggressive behavior in isolated mice (ID_{50} = 1.2 mg/kg s.c.). Moreover, in a rat chronic mild stress model, it enhanced sucrose consumption in a dose- (2.5-40 mg/kg s.c.) and time-dependent manner. In a learned helplessness paradigm in rats, the dose of 10 mg/kg s.c. significantly reduced escape failure and increased intertrial crossings. In addition, compound induced loss of righting reflex in rats (ED_{50} = 0.4 mg/kg s.c.) and generalized to citalopram in a discriminative stimulus generalization test (ED_{50} = 0.1 mg/kg s.c.). Motor behavior was marginally affected by compound only at the highest doses. Overall, these results indicate a pharmacological profile similar to that of venlafaxine and clomipramine, but with improved potency.

SOURCE – Servier.

REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) *Benzocyclobutan cpds., their process for preparation and pharmaceutical compsns. containing them*. CA 2264372, EP 0940386, FR 2775687, JP 1999310557, US 6107345.

2. Brocco, M.J. et al. *S33005, a potent inhibitor of serotonin and noradrenaline uptake: II. Antidepressant profile in comparison to citalopram, reboxetine, venlafaxine and clomipramine*. Soc Neurosci Abst 2000, 26(Part 2): Abst 624.8.

3. Millan, M.J. et al. *S33005, a novel ligand at both serotonin and norepinephrine transporters: I. Receptor binding, electrophysiological, and neurochemical profile in comparison with venlafaxine, reboxetine, citalopram, and clomipramine*. J Pharmacol Exp Ther 2001, 298(2): 565.

4. Millan, M.J. et al. *S33005, a novel ligand at both serotonin and norepinephrine transporters: II. Behavioral profile in comparison with venlafaxine, reboxetine, citalopram, and clomipramine*. J Pharmacol Exp Ther 2001, 298(2): 581.

5. Millan, M.J. et al. *S33005, a potent inhibitor of serotonin and noradrenaline uptake: I. Influence upon monoaminergic transmission in comparison to citalopram, reboxetine, venlafaxine and clomipramine*. Soc Neurosci Abst 2000, 26(Part 2): Abst 624.9.

6. Peglion, J.-L. et al. *S 33005, a novel ligand at both serotonin and norepinephrine transporters, as a potential improved treatment for depression*. 2nd Int Forum Mood Anxiety Disord (Nov 28-Dec 1, Monte-Carlo) 2001, Abst.

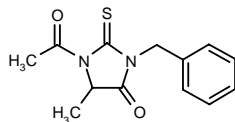
*Identified compound **280913** Drug Data Rep 1999, 021(11): 0963.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

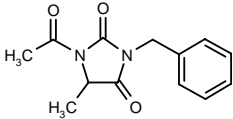
310423

1-Acetyl-3-benzyl-5-methyl-2-thioxoimidazolidin-4-one



C13 H14 N2 O2 S; Mol wt: 262.3316

ACTION – Anticonvulsant shown to afford significant protection against s.c. metrazol-induced seizures in mice (ED_{50} = 46 mg/kg i.p.) and maximal electroshock (MES) seizures in rats (ED_{50} = 12 mg/kg i.p.). Low neurotoxicity was seen in mice on the rotarod test (ED_{50} = 120 mg/kg i.p.). Another related compound is:



310422: C13 H14 N2 O3

SOURCES – University of Houston, Houston, TX (US); National Institutes of Health, Bethesda, MD (US); University of North Carolina, Chapel Hill, NC (US).

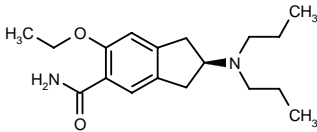
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1. Le Tiran, A. et al. *Functionalized amino acid anticonvulsants: Synthesis and pharmacological evaluation of conformationally restricted analogues*. Bioorg Med Chem 2001, 9(10): 2693.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

309353

(+)-2(S)-(Dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxamide



C18 H28 N2 O2; Mol wt: 304.4312

ACTION – A selective dopamine D3 antagonist with potential in the treatment of CNS disorders including anxiety, obesity, depression, schizophrenia, stress-related disorders, panic and sleep disorders, phobias, obsessive-compulsive disorder, posttraumatic syndrome, sexual dysfunction, attention deficit hyperactivity disorder, migraine, substance abuse and cognition disorders, among others, particularly for drug or nicotine abuse and movement disorders such as Parkinson's disease and Huntington's disease.

SOURCE – Pharmacia.

REFERENCES

1. Runge, T.A. et al. (Pharmacia Corp.) *(2S)-Aminoindan derivs., a process for their preparation and their use as selective dopamine D3 ligands*. WO 0162712.

firing of neurons in the locus ceruleus. Consistent with its binding, electrophysiological and neurochemical profile, the compound showed strong efficacy in behavioral experiments predictive of antidepressant activity including the forced swimming and tail-suspension tests in mice (ID_{50} = 7.4 and 6.8 mg/kg s.c., respectively), marble-burying behavior in mice (ID_{50} = 3.5 mg/kg s.c.) and aggressive behavior in isolated mice (ID_{50} = 1.2 mg/kg s.c.). Moreover, in a rat chronic mild stress model, it enhanced sucrose consumption in a dose- (2.5-40 mg/kg s.c.) and time-dependent manner. In a learned helplessness paradigm in rats, the dose of 10 mg/kg s.c. significantly reduced escape failure and increased intertrial crossings. In addition, compound induced loss of righting reflex in rats (ED_{50} = 0.4 mg/kg s.c.) and generalized to citalopram in a discriminative stimulus generalization test (ED_{50} = 0.1 mg/kg s.c.). Motor behavior was marginally affected by compound only at the highest doses. Overall, these results indicate a pharmacological profile similar to that of venlafaxine and clomipramine, but with improved potency.

SOURCE – Servier.

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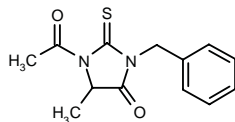
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

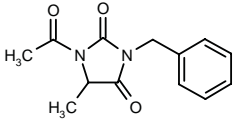
310423

1-Acetyl-3-benzyl-5-methyl-2-thioxoimidazolidin-4-one



C13 H14 N2 O2 S; Mol wt: 262.3316

ACTION – Anticonvulsant shown to afford significant protection against s.c. metrazol-induced seizures in mice (ED_{50} = 46 mg/kg i.p.) and maximal electroshock (MES) seizures in rats (ED_{50} = 12 mg/kg i.p.). Low neurotoxicity was seen in mice on the rotarod test (ED_{50} = 120 mg/kg i.p.). Another related compound is:



310422: C13 H14 N2 O3

SOURCES – University of Houston, Houston, TX (US); National Institutes of Health, Bethesda, MD (US); University of North Carolina, Chapel Hill, NC (US).

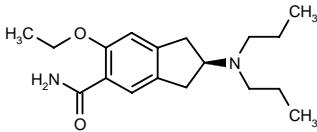
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

309353

(+)-2(S)-(Dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxamide



C18 H28 N2 O2; Mol wt: 304.4312

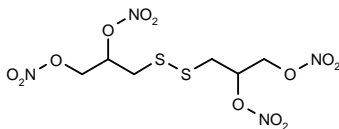
ACTION – A selective dopamine D3 antagonist with potential in the treatment of CNS disorders including anxiety, obesity, depression, schizophrenia, stress-related disorders, panic and sleep disorders, phobias, obsessive-compulsive disorder, posttraumatic syndrome, sexual dysfunction, attention deficit hyperactivity disorder, migraine, substance abuse and cognition disorders, among others, particularly for drug or nicotine abuse and movement disorders such as Parkinson's disease and Huntington's disease.

SOURCE – Pharmacia.

REFERENCES

1. Runge, T.A. et al. (Pharmacia Corp.) *(2S)-Aminoindan derivs., a process for their preparation and their use as selective dopamine D3 ligands*. WO 0162712.

GT-715

310835**3,3'-Disulfanylbis-1,2-propanediol tetranitrate**C₆ H₁₀ N₄ O₁₂ S₂; Mol wt: 394.2930

ACTION – Neuroprotective agent, a nitrate ester able to protect dopaminergic neurons from 6-OHDA toxicity in a rat model of Parkinson's disease; at 200 µmol/kg s.c. every hour for 6 h starting 30 min before unilateral injection of 6-OHDA into the substantia nigra, it protected animals from apomorphine-induced rotations and preserved substantia nigra tyrosine hydroxylase-positive neurons from 6-OHDA toxicity. In another study, compound (5-50 µmol/kg s.c.) was found to reverse the cognitive impairment caused by scopolamine in the Morris water maze test in rats. Potentially useful for the treatment of neurodegenerative disorders including Parkinson's disease and stroke.

SOURCES – GoBang Therapeutics; Queen's University, Kingston, ON (CA).

REFERENCES

1. Thatcher, G.R. et al. (Queen's University) *Nitrate esters and their use for neurological conditions*. US 5807847, WO 9746521.
2. Thatcher, G.R.J. et al. (Queen's University) *Methods and compsns. for mitigating pain*. WO 0149275.
3. Thatcher, G.R.J. et al. (Queen's University) *Nitrate esters and their use for neurological conditions*. US 5883122.
4. Thatcher, G.R.J. et al. (Queen's University) *Nitrate esters and their use for neurological conditions*. WO 0054756.
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TREATMENT OF NEURODEGENERATIVE DISORDERS

Fab D18

307032**Recombinant antigen-binding fragment (Fab) of antibody D18 specific for prion protein**

ACTION – Prion protein-specific antibody fragment able to completely abolish the propagation of the scrapie isoform of prion protein (PrP^{Sc}) in PrP-infected mouse neuroblastoma cells. This antibody at a concentration of 10 µM rapidly cleared preexisting PrP^{Sc} from cells, suggesting that it may cure established infections. The potent activity of the antibody is associated with its ability to block the interaction of PrP^{Sc} with cellular prion protein. Potentially useful for the treatment of prion diseases.

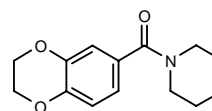
SOURCES – University of California, San Francisco, San Francisco, CA (US); Scripps Research Institute, La Jolla, CA (US).

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1. Leclerc, E. et al. *Immobilized prion protein undergoes spontaneous rearrangement to a conformation having features in common with the infectious form*. EMBO J 2001, 20(7): 1547.
2. Peretz, D. et al. *Antibodies inhibit prion propagation and clear cell cultures of prion infectivity*. Nature 2001, 412: 739.
3. Williamson, R.A. et al. *Mapping the prion using recombinant antibodies*. J Virol 1998, 72(11): 9413.

TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

CX-546

283057**1-(2,3-Dihydro-1,4-benzodioxin-6-ylcarbonyl)piperidine**C₁₄ H₁₇ N O₃; Mol wt: 247.2923

ACTION – Positive modulator of AMPA-type glutamate receptors, or ampakine, proven to counteract behavior resulting from dopaminergic imbalance. Compound significantly suppressed dopamine-mediated rotation in rats, and in knockout mice lacking the dopamine transporter (DAT-KO mice), a transgenic mouse model of attention deficit hyperactivity disorder (ADHD), it dose-dependently (30-70 mg/kg s.c.) decreased horizontal and vertical activities in a novel environment. Potentially useful for the treatment of ADHD, as well as schizophrenia.

SOURCES – University of California, Oakland, CA (US); Cortex.

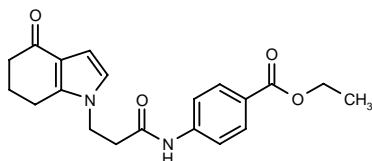
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4. Hess, U.S. et al. *Ampakine suppression of dopamine-mediated rotation: Implications for treatment of schizophrenia*. Soc Neurosci Abst 1999, 25(Part 2): Abst 815.2.
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6. Lauterborn, J.C. et al. *Positive modulation of AMPA receptors increases neutrophin expression by hippocampal and cortical neurons*. J Neurosci 2000, 20(1): 8.

NEO-339

310974

4-[3-(4-Oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)propion-amido]benzoic acid ethyl ester



C20 H22 N2 O4; Mol wt: 354.4038

ACTION – Heterocyclic purine mimetic related to Neotrofin™ (leteprinim potassium), able to improve attention deficits and learning and memory in aged and young mice. In young mice, compound dose-dependently attenuated cycloheximide-induced passive avoidance task performance deficits with an ED₅₀ of 0.0003 mg/kg, without interfering with activity levels or motor function. In aged mice with severe learning deficits, compound produced significant improvement in acquisition of an active avoidance task, as well as long-lasting improvement in sensorimotor reactivity, and markedly improved awareness, in the absence of effects on activity or motor function. Potentially useful for the treatment of attention deficit disorders and mild cognitive impairment.

SOURCE – NeoTherapeutics.

REFERENCES

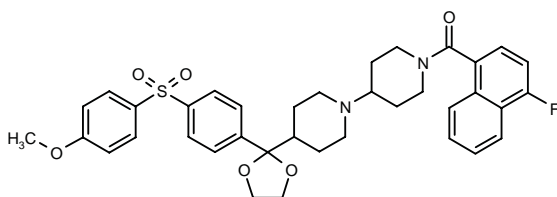
1. Helton, D.R. et al. *Effect of NEO-339 on learning, memory and sensorimotor responsiveness in young and aged mice*. Soc Neurosci Abst 2001, 27: Abst 78.17.
2. *NeoTherapeutics continues to accomplish milestone objectives*. DailyDrugNews.com (Daily Essentials) 2001, Nov 21.

TREATMENT OF COGNITION DISORDERS

307998

1'-(4-Fluoronaphthalen-1-ylcarbonyl)-4-[2-[4-(4-methoxyphenylsulfonyl)phenyl]-1,3-dioxolan-2-yl]-1,4'-bipiperidine

1-(4-Fluoronaphthalen-1-yl)-1-[4-[2-[4-(4-methoxyphenylsulfonyl)phenyl]-1,3-dioxolan-2-yl]-1,4'-bipiperidin-1'-yl]methanone



C37 H39 F N2 O6 S; Mol wt: 658.7871

ACTION – Muscarinic M₂ receptor antagonist with subnanomolar affinity for M₂ receptors (K_i = 0.51 nM) and at least 100-fold selectivity over M₁ and M₃ receptors. Compound exhibited stability in human microsomes and oral bioavailability in rodents and primates. *In vivo*, a significant increase in acetylcholine release in rat striatum was seen at a dose of 10 mg/kg p.o. and cognitive improvement was obtained at doses of 0.1 and 0.3 mg/kg p.o. in the rat passive avoidance test. Potentially useful for the treatment of Alzheimer's disease.

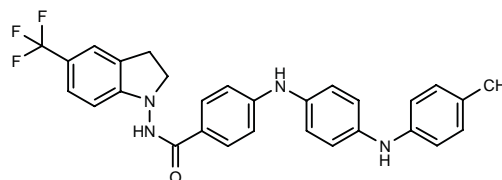
SOURCE – Schering-Plough.

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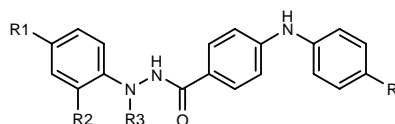
308801

4-[4-(4-Methylphenylamino)phenylamino]-*N*-[5-(trifluoromethyl)-2,3-dihydro-1*H*-indol-1-yl]benzamide



C29 H25 F3 N4 O; Mol wt: 502.5375

ACTION – An inhibitor of β -amyloid aggregation found to inhibit the aggregation of synthetic β -amyloid(1-40) peptide with an IC₅₀ of 0.29 μ M, and lipid autooxidation in mouse brain homogenate with an IC₅₀ of 0.1 μ M. Potentially useful for the treatment and prevention of dementia, particularly Alzheimer's dementia. Other exemplified *N*-arylhydrazide compounds include the following:



Compound	R1	R2	R3	R4	Formula
308802	CF3	H	H	4-Me-PhNH	C ₂₇ H ₂₃ F ₃ N ₄ O
308803	Me	-(CH2)2-		4-Me-PhNH	C ₂₈ H ₂₈ N ₄ O
308804	H	H	H	H	C ₁₉ H ₁₇ N ₃ O
308805	H	NO2	H	H	C ₁₉ H ₁₆ N ₄ O ₃
308806	CF3	H	H	H	C ₂₀ H ₁₆ F ₃ N ₃ O
308807	H	-(CH2)2-		H	C ₂₁ H ₁₉ N ₃ O
308808	H	H	H	NHPh	C ₂₅ H ₂₂ N ₄ O
308809	CF3	H	H	NHPh	C ₂₆ H ₂₁ F ₃ N ₄ O
308810	Me	H	H	4-Me-PhNH	C ₂₇ H ₂₆ N ₄ O
308811	Me	-CH=CH-		4-Me-PhNH	C ₂₈ H ₂₆ N ₄ O

SOURCE – Japan Tobacco.

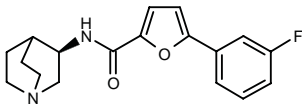
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308913

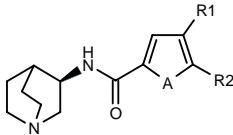
N-[1-Azabicyclo[2.2.2]oct-3(*R*)-yl]-5-(3-fluorophenyl)-furan-2-carboxamide

5-(3-Fluorophenyl)-*N*-[quinuclidin-3(*R*)-yl]furan-2-carboxamide

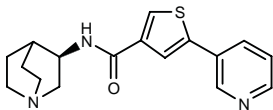


C18 H19 F N2 O2; Mol wt: 314.3581

ACTION – Selective $\alpha 7$ nicotinic acetylcholine receptor (nAChR) ligand with potential for the treatment or prophylaxis of schizophrenia, anxiety, mania, manic depression, Alzheimer’s disease, learning deficits, attention deficit hyperactivity disorder, memory loss, Parkinson’s disease, Huntington’s disease, Tourette’s syndrome, jet lag, smoking cessation, pain and ulcerative colitis. Other specifically claimed compounds from this series of biarylcarboxamides include the following:



Compound	R1	R2	A	Formula
308915	H	3-Pyr	O	C ₁₇ H ₁₉ N ₃ O ₂
308916	H	4-F-Ph	O	C ₁₈ H ₁₉ FN ₂ O ₂
308918	H	3-AcNH-Ph	O	C ₂₀ H ₂₃ N ₃ O ₃
308919	H	3-Cl-Ph	O	C ₁₈ H ₁₉ ClN ₂ O ₂
308922	Ph	H	S	C ₁₈ H ₂₀ N ₂ OS
308923	H	3-(CH2OH)-Ph	S	C ₁₉ H ₂₂ N ₂ O ₂ S



308920: C17 H19 N3 O S

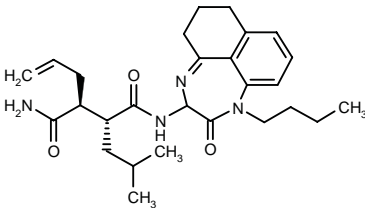
SOURCE – AstraZeneca.

REFERENCES

1. Phillips, E. and Schmiesing, R. (AstraZeneca AB) *Novel biarylcarboxamides*. WO 0160821.

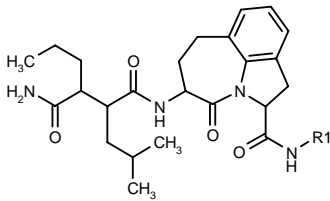
309060

3(*S*)-Allyl-*N*¹-(4-butyl-3-oxo-2,3,4,8,9,10-hexahydronaphtho[1,8-*ef*][1,4]diazepin-2-yl)-2(*R*)-isobutylsuccinamide

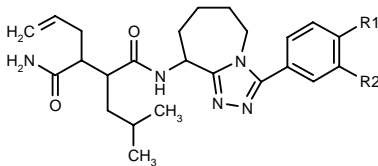


C27 H38 N4 O3; Mol wt: 466.6222

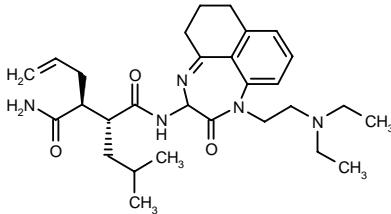
ACTION – Agent with the ability to inhibit the production of β -amyloid peptide (A β) through an interaction with β - and/or γ -secretase. Potentially useful for the treatment of Alzheimer’s disease. Other specifically claimed succinamido-containing carbocycles include the following:



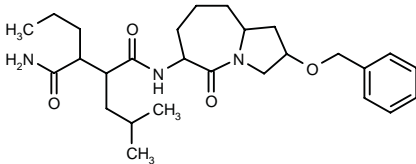
Compound	R1	Formula
309062	1-(PhCH2)-3-pyrrolidinyl	C ₃₅ H ₄₇ N ₅ O ₄
309063	Ph	C ₃₀ H ₃₈ N ₄ O ₄



Compound	R1	R2	Formula
309065	Br	H	C ₂₄ H ₃₂ BrN ₅ O ₂
309066	3,5-(Me)2-4-isoxazolyl	H	C ₂₉ H ₃₈ N ₆ O ₃
309067	H	2-benzofuryl	C ₃₂ H ₃₇ N ₅ O ₃



309061: C29 H43 N5 O3



309064: C27 H41 N3 O4

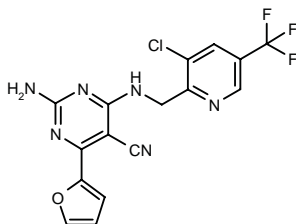
SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

REFERENCES

1. Olson, R.E. et al. (DuPont Pharmaceuticals Co.) *Succinoylamino carbocycles and heterocycles as inhibitors of A beta protein production*. WO 0160826.

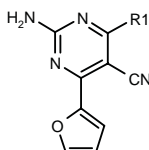
309380

2-Amino-4-[3-chloro-5-(trifluoromethyl)pyridin-2-ylmethylamino]-6-(2-furyl)pyrimidine-5-carbonitrile



C₁₆H₁₀ClF₃N₆O; Mol wt: 394.7430

ACTION – Adenosine receptor modulator with pK_i values of 5.35, 8.44 and 5.02 against the human A₁, A₂ and A₃ receptor subtypes, respectively. Potentially useful for the treatment of Alzheimer's disease, Parkinson's disease, neurodegeneration, schizophrenia, anxiety, pain, respiratory deficits, depression, asthma, allergic responses, hypoxia, ischemia, seizures, substance abuse, and as a muscle relaxant, anticonvulsant and cardioprotective agent. Other exemplified compounds are:



Compound	R1	Formula
309381	2-Naph-CH ₂ NH	C ₂₀ H ₁₅ N ₅ O
309383	2-Naph-CH ₂ O	C ₂₀ H ₁₄ N ₄ O ₂
309384	4-CF ₃ -PhCH ₂ NH	C ₁₇ H ₁₂ F ₃ N ₅ O

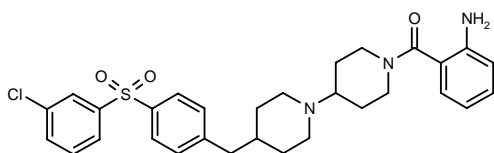
SOURCE – Roche.

REFERENCES

1. Borroni, E.M. et al. (F. Hoffmann-La Roche AG) *Adenosine receptor modulators*. WO 0162233.

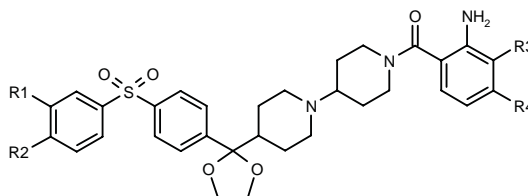
309388

1-(2-Aminophenyl)-1-[4-[4-(3-chlorophenylsulfonyl)-benzyl]-1,4'-bipiperidin-1'-yl]methanone



C₃₀H₃₄ClN₃O₃S; Mol wt: 552.1356

ACTION – A selective muscarinic M₂ receptor antagonist giving a K_i of 0.225 nM against the M₂ receptor subtype and exhibiting over 2,900-, 2,700-, 140- and 180-fold selectivity over the M₁, M₃, M₄ and M₅ receptor subtypes, respectively. Potentially useful for the treatment of cognitive and neurodegenerative diseases including Alzheimer's disease and senile dementia. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
309390	H	OMe	Me	H	C ₃₄ H ₄₇ N ₃ O ₆ S
309391	Cl	H	H	F	C ₃₂ H ₃₅ ClFN ₃ O ₆ S
309392	H	OMe	F	H	C ₃₃ H ₃₈ FN ₃ O ₆ S

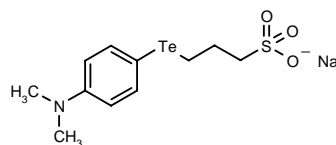
SOURCE – Schering-Plough.

REFERENCES

1. Clader, J.W. et al. (Schering Corp.) *Muscarinic antagonists*. US 6294554.

310357

3-[4-(Dimethylamino)phenyltellanyl]propane-1-sulfonic acid sodium salt



C₁₁H₁₆NNaO₃STe; Mol wt: 392.9074

ACTION – Water-soluble antioxidant, an organotellurium compound with excellent reactivity towards hydrogen peroxide and/or hydroxyl radicals in solution. Compound protected proteins and lipids from oxidative stress in various systems including red blood cells, synaptosomal membranes and cultured neuronal cells, and is an excellent candidate for the treatment of oxidative stress-related neurodegenerative disorders including Alzheimer's disease.

SOURCES – University of Kentucky, Lexington, KY (US); Uppsala University, Uppsala (SE).

REFERENCES

1. Engman, L. et al. *Water-soluble organotellurium compounds inhibit thioredoxin reductase and the growth of human cancer cells*. *Anti-Cancer Drug Des* 2000, 15(5): 323.

2. Hanski, J. et al. *Antioxidant activity of the organotellurium compound 3-[4-(N,N-dimethylamino) benzenetellurenyl]propanesulfonic acid against oxidative stress in synaptosomal membrane systems and neuronal cultures*. *Soc Neurosci Abst* 2001, 27: Abst 549.19.

3. Jacob, C. et al. *Water-soluble organotellurium compounds: Catalytic protection against peroxynitrite and release of zinc from metallothionein*. *Chem Res Toxicol* 2000, 13(1): 3.

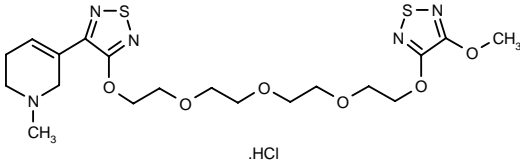
4. Kanda, T. et al. *Novel water-soluble diorganyl tellurides with thiol peroxidase and antioxidant activity*. *J Org Chem* 2001, 64(22): 8161.

5. Kanski, J. et al. *Antioxidant activity of the organotellurium compound 3-[4-(N,N-dimethylamino)benzenetellurenyl]propanesulfonic acid against oxidative stress in synaptosomal membrane systems and neuronal cultures*. *Brain Res* 2001, 911(1): 12.

CDD-0304

310670

5-[4-[2-[2-[2-[2-(4-Methoxy-1,2,5-thiadiazol-3-yloxy)ethoxy]ethoxy]ethoxy]ethoxy]-1,2,5-thiadiazol-3-yl]-1-methyl-1,2,3,6-tetrahydropyridine hydrochloride



C19 H29 N5 O6 S2 . HCl; Mol wt: 524.0600

ACTION – Potent and selective muscarinic M₁ receptor agonist with nanomolar affinity for the receptor (K_i = 38 nM) and excellent agonist activity, stimulating phosphoinositide metabolism to a maximum of 600% over baseline (62% of carbachol effect; EC₅₀ = 64 nM). Compound, is expected to penetrate the CNS and is a useful lead for the design of new treatments for Alzheimer’s disease.

SOURCES – Cognitive Pharmaceuticals; University of Toledo, Toledo, OH (US).

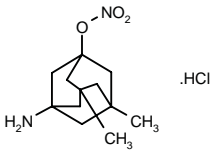
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1. Cao, Y. et al. *Synthesis and biological evaluation of tetrahydropyridyl-thiadiazole derivatives as selective M1 muscarinic agonists for the treatment of Alzheimer's disease.* Soc Neurosci Abst 2001, 27: Abst 912.1.

TREATMENT OF CEREBROVASCULAR DISEASES

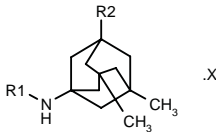
309356

3-Amino-5,7-dimethyladamant-1-yl nitrate hydrochloride



C12 H20 N2 O3 . HCl; Mol wt: 276.7619

ACTION – Neuroprotective agent potentially useful for the treatment of stroke, hypoglycemic neuronal damage, cerebral ischemia, cardiac arrest, spinal cord trauma, head trauma and perinatal hypoxia. *In vitro*, the compound displayed a protective effect against NMDA-induced damage of cerebrocortical neurons. *In vivo*, it demonstrated neuroprotective activity in a mouse model of cerebral ischemia following i.p. administration. Other exemplified aminoadamantane derivatives include the following:



Compound	R1	R2	X	Formula
309365	Ac	CO2H		C ₁₅ H ₂₃ NO ₃
309366	Ac	CH2OH		C ₁₅ H ₂₅ NO ₂
309367	H	CH2OH	HCl	C ₁₃ H ₂₃ NO.HCl
309368	H	CH2ONO2	HBr	C ₁₃ H ₂₂ N ₂ O ₃ .HBr

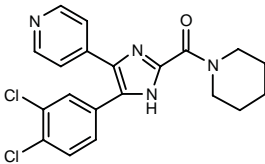
SOURCE – Panorama Research.

REFERENCES

1. Wang, Y. et al. (Panorama Research, Inc.) *Aminoadamantane derivs. as therapeutic agents.* WO 0162706.

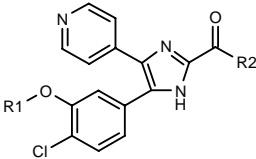
310117

1-[5-(3,4-Dichlorophenyl)-4-(4-pyridyl)-1*H*-imidazol-2-yl]-1-(1-piperidinyl)methanone



C20 H18 Cl2 N4 O; Mol wt: 401.2952

ACTION – An inhibitor of Raf kinases, in particular B-Raf kinase, with potential for the treatment or prevention of neurotraumatic disorders such as head trauma and ischemic stroke, as well as cancer. A representative compound from a series of imidazol-2-carboxamide derivatives, wherein the following are also included:



Compound	R1	R2	Formula
310118	Me	1-Pip	C ₂₁ H ₂₁ ClN ₄ O ₂
310119	H	1-Pip	C ₂₀ H ₁₉ ClN ₄ O ₂
310120	H	NHCH2CH2N(Me)2	C ₁₉ H ₂₀ ClN ₅ O ₂

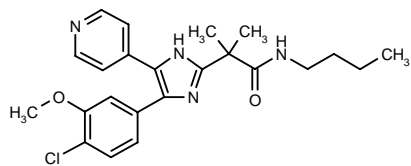
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gaiba, A. et al. (SmithKline Beecham plc) *Imidazol-2-carboxamide derivs. as Raf kinase inhibitors.* WO 0166540.

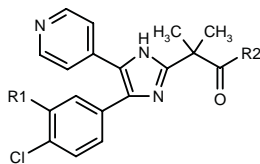
310122

N-Butyl-2-[4-(4-chloro-3-methoxyphenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]-2-methylpropionamide



C23 H27 Cl N4 O2; Mol wt: 426.9453

ACTION – An inhibitor of Raf kinases, in particular B-Raf kinase, with potential for the treatment or prevention of neurotraumatic disorders such as head trauma and ischemic stroke, as well as cancer. A representative compound from a series of imidazole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
310123	OH	NHBU	C ₂₂ H ₂₅ ClN ₄ O ₂
310124	Cl	4-morpholinyl	C ₂₂ H ₂₂ Cl ₂ N ₄ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

1. Steadman, J.G. and Takle, A.K. (SmithKline Beecham plc) *Imidazol derivs. as Raf kinase inhibitors*. WO 0166539.

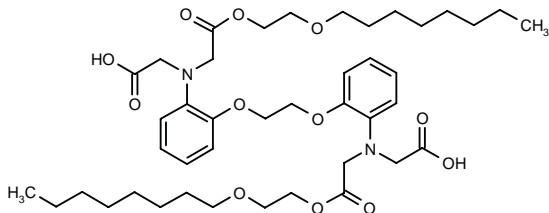
DP-B99

278687

2,2'-(Ethylenedioxy)bis(2,1-phenylene)bis[N-[2-[2-(octyloxy)ethoxy]-2-oxoethyl]imino]bis(acetic acid)

N,N'-[1,2-Ethanediy]bis(oxy-2,1-phenylene)]bis[N-(carboxymethyl)glycine] 1,1'-bis[2-(octyloxy)ethyl] ester

DP-BAPTA-99



C42 H64 N2 O12; Mol wt: 788.9696

ACTION – Neuroprotective agent, a lipophilic membrane-activated chelator of divalent metal ions such as Ca²⁺, Cu²⁺, Zn²⁺ and Fe²⁺, proven to modulate cell calcium homeostasis. In a model of transient forebrain ischemia in Mongolian gerbils, compound (10 µg/kg i.p.) given pre- or postischemia showed a significant protective effect in the CA2 and CA3 regions of the hippocampus. Significant neuroprotection was also demonstrated in transient and permanent middle cerebral artery occlusion (MCAO) models in rats (70-90% reduction of infarct size) and this effect was sustained even when compound was administered 8 h after ischemic insult. Neurological outcome was significantly improved by compound in all studies and behavioral deficits in the animals subjected to global cerebral ischemia were also improved. Standard preclinical toxicology studies in rats and dogs demonstrated that compound is safe, with no cardiotoxicity. In a phase I clinical trial in healthy volunteers it was safe and well tolerated at doses of 3-1000 µg/kg i.v. and no cardiovascular or CNS side effects were seen, even at the highest dose; phase II clinical studies are in progress in patients with acute stroke.

SOURCE – D-Pharm.

REFERENCES

1. Kozak, A. and Shapiro, I. (D-Pharm Ltd.) *Lipophilic diesters of chelating agents*. JP 2001518458, WO 9916741.

2. Kalendarev, T. et al. *The unusual gradient elution for reversed phase HPLC of a strong chelator as an active drug substance*. J Pharm Biomed Anal 2001, 24(5-6): 967.

3. Krakovsky, M. et al. *DP-b99 ameliorates brain damage and improves outcome in both focal and global cerebral ischemic injuries*. 17th World Congr Neurol (June 17-22, London) 2001, Abst P0733.

4. Krakovsky, M. et al. *DP-B99: A novel membrane-targeted compound with neuroprotective action in global and focal cerebral ischemia*. J Cereb Blood Flow Metab 1999, 19(Suppl. 1): Abst 821.

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7. *D-Pharm completes toxicity testing of DP-b99 in preparation for phase I trials later this year*. DailyDrugNews.com (Daily Essentials) 1999, Nov 10.

8. *D-Pharm's DP-b99 successfully completes phase I study as treatment of acute stroke*. DailyDrugNews.com (Daily Essentials) 2000, Aug 4.

9. *D-Pharm's neuroprotective drug candidate nears phase II*. DailyDrugNews.com (Daily Essentials) 2000, Oct 17.

10. *DP-b99 enters phase I testing in Germany*. DailyDrugNews.com (Daily Essentials) 2000, March 7.

11. *Novel chelator designed by D-Pharm commences phase II clinical development for stroke*. DailyDrugNews.com (Daily Essentials) 2001, Sept 14.

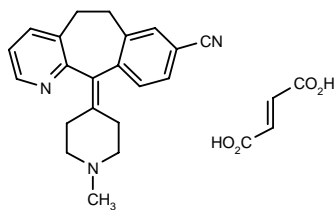
RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

SS-212*

187346

11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridine-8-carbonitrile fumarate



C21 H21 N3 . C4 H4 O4; Mol wt: 431.4895

ACTION – Potent and selective histamine H₁ antagonist with an EC₅₀ value of 10.3 nM for inhibition of histamine-induced contractions in guinea pig ileum and an EC₅₀ of 26.6 μM using acetylcholine as the agonist (antihistaminic selectivity = 2,600). *In vivo*, compound induced a dose-dependent and long-lasting inhibition of histamine-induced vascular permeability and the passive cutaneous anaphylaxis (PCA) reaction in guinea pigs (ED₅₀ = 0.013 and 0.022 mg/kg p.o., respectively). Moreover, it inhibited the histamine-induced increase in nasal cavity pressure and PAF-induced airways contraction, but was inactive against LTD₄ and TxA₂. Compound did not exhibit a central action, evaluated by measuring its ability to prolong pentobarbital-induced sleeping time in mice (up to 10 mg/kg), and it did not inhibit pentylenetetrazol-induced convulsions at up to 300 mg/kg. Potentially useful as an antiallergic agent.

SOURCE – SSP.

REFERENCES

1. Honda, H. et al. (SSP Co., Ltd.) *Novel benzo[5,6]cyclohepta[1,2-*b*]pyridine derivs. and antiallergic agents comprising same*. EP 0495484, JP 1993059040, US 5231101.

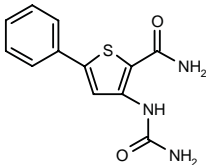
2. Iwase, N. et al. *Pharmacological property of SS 212 a novel anti-allergic drug*. Folia Pharmacol Jpn 2001, 118(4): Abst 3-4.

*Identified compound **187346** Drug Data Rep 1993, 015(02): 0148.

ASTHMA THERAPY

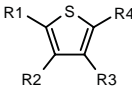
308812

5-Phenyl-3-ureidothiophene-2-carboxamide



C12 H11 N3 O2 S; Mol wt: 261.3039

ACTION – Agent with the ability to regulate the activation of NF-κB through inhibition of IκB kinase-2 (IKK-2). Potentially useful for the treatment of inflammatory diseases, particularly asthma, rheumatoid arthritis, multiple sclerosis and chronic obstructive pulmonary disease (COPD). Other specifically claimed heterocyclic carboxamides are:



Compound	R1	R2	R3	R4	Formula
308813	2-Cl-Ph	H	NHCONH2	CONH2	C ₁₂ H ₁₀ ClN ₃ O ₂ S
308814	3-(1-Pip- -CH2CH2O)-Ph	H	NHCONH2	CONH2	C ₁₉ H ₂₄ N ₄ O ₃ S
308815	4-Me-Ph	Me	CONH2	NHCONH2	C ₁₄ H ₁₅ N ₃ O ₂ S
308816	4-MeO-3-Me-Ph	Me	CONH2	NHCONH2	C ₁₅ H ₁₇ N ₃ O ₃ S
308817	4-CF3-Ph	H	CONH2	NHCONH2	C ₁₃ H ₁₀ F ₃ N ₃ O ₂ S
308819	3-furyl	H	CONH2	NHCONH2	C ₁₀ H ₈ N ₃ O ₃ S
308820	4-(4-thiazolyl- -CH2O)-Ph	H	CONH2	NHCONH2	C ₁₆ H ₁₄ N ₄ O ₃ S ₂
308821	Ph	H	CONH2	NHCSNH2	C ₁₂ H ₁₁ N ₃ OS ₂

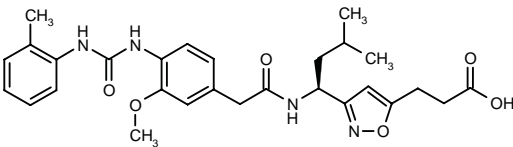
SOURCE – AstraZeneca.

REFERENCES

1. Baxter, A. et al. (AstraZeneca AB) *Heteroaromatic carboxamide derivs. and their use as inhibitors of the enzyme IKK-2*. WO 0158890.

308877

3-[3-[1 (*S*)-[2-[3-Methoxy-4-[3-(2-methylphenyl)-ureido]phenyl]acetamido]-3-methylbutyl]isoxazol-5-yl]-propionic acid



C28 H34 N4 O6; Mol wt: 522.5986

ACTION – Potent integrin $\alpha_4\beta_1$ antagonist with an IC₅₀ value of 10.3 nM in a receptor/ligand assay and IC₅₀ values of 0.69-1.0 nM in cellular assays in Jurkat cells and human eosinophils. In an allergic mouse model, a dose of 10 mg/kg s.c. produced a 58% reduction of eosinophils in bronchoalveolar lavage fluid; an ED₅₀ of 2 µg/kg was obtained following intratracheal instillation. Potentially useful for the treatment of asthma.

SOURCE – Pfizer.

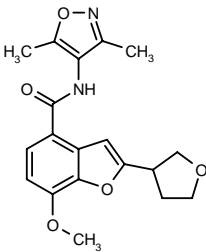
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2. Duplantier, A.J. et al. *Isoxazolyl, oxazolyl, and thiazolylpropionic acid derivatives as potent $\alpha_4\beta_1$ integrin antagonists*. Bioorg Med Chem Lett 2001, 11(19): 2593.

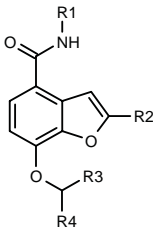
308887

N-(3,5-Dimethylisoxazol-4-yl)-7-methoxy-2-(tetrahydrofuran-3-yl)-1-benzofuran-4-carboxamide



C19 H20 N2 O5; Mol wt: 356.3760

ACTION – An inhibitor of TNF production and phosphodiesterase type 4 (PDE4) activity, potentially useful for the treatment of inflammatory and autoimmune diseases, particularly asthma, chronic obstructive pulmonary disease (COPD) and chronic bronchitis. Other specifically claimed benzofuran carboxamides are:



Compound	R1	R2	R3	R4	Formula
308888	4-CN-1-Me-5-imidazolyl	CH2OMe	H	H	C ₁₇ H ₁₆ N ₄ O ₄
308890	4-CN-1-Me-5-pyrazolyl	3-THF	H	H	C ₁₉ H ₁₈ N ₄ O ₄
308891	4-CN-1-Me-5-pyrazolyl	CH2OMe	H	H	C ₁₇ H ₁₆ N ₄ O ₄
308892	3,5-(Me)2-4-isoxazolyl	2-THF	H	H	C ₁₉ H ₂₀ N ₂ O ₅
308893	4-Cl-1-Me-5-pyrazolyl	CH2OMe	H	H	C ₁₆ H ₁₆ ClN ₃ O ₄
308894	1-Et-5-pyrazolyl	CH2OMe	H	H	C ₁₇ H ₁₉ N ₃ O ₄
308895	3,5-(Me)2-4-isoxazolyl	CH2OMe	F	F	C ₁₇ H ₁₆ F ₂ N ₂ O ₅

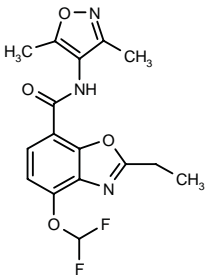
SOURCE – Darwin Discovery.

REFERENCES

1. Dyke, H.J. et al. (Darwin Discovery Ltd.) *Benzofuran carboxamides and their therapeutic use*. US 6331556, WO 0158895.

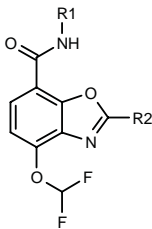
308896

4-(Difluoromethoxy)-*N*-(3,5-dimethylisoxazol-4-yl)-2-ethylbenzoxazole-7-carboxamide



C16 H15 F2 N3 O4; Mol wt: 351.3075

ACTION – An inhibitor of TNF production and phosphodiesterase type 4 (PDE4) activity, potentially useful for the treatment of inflammatory and autoimmune diseases, particularly asthma, chronic obstructive pulmonary disease (COPD) and chronic bronchitis. Other specifically claimed benzoxazole derivatives are:



Compound	R1	R2	Formula
308898	3-Et-5-Me-4-isoxazolyl	Et	C ₁₇ H ₁₇ F ₂ N ₃ O ₄
308899	1-Me-5-pyrazolyl	Et	C ₁₅ H ₁₄ F ₂ N ₄ O ₃
308900	1-Et-5-pyrazolyl	Et	C ₁₆ H ₁₆ F ₂ N ₄ O ₃
308901	4-CN-1-Me-5-imidazolyl	Et	C ₁₆ H ₁₃ F ₂ N ₅ O ₃
308902	4-CN-1-Me-5-pyrazolyl	4-morpholinyl	C ₁₈ H ₁₆ F ₂ N ₆ O ₄
308903	4-CN-1-Me-5-pyrazolyl	1-Pip	C ₁₉ H ₁₈ F ₂ N ₆ O ₃
308904	4-Cl-1-Me-5-pyrazolyl	Et	C ₁₅ H ₁₃ ClF ₂ N ₄ O ₃
308905	3-CF3-5-Me-4-isoxazolyl	Et	C ₁₆ H ₁₂ F ₅ N ₃ O ₄

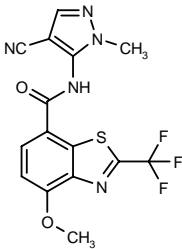
SOURCE – Darwin Discovery.

REFERENCES

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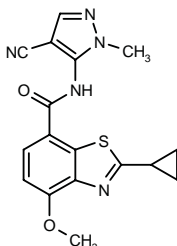
308906

N-(4-Cyano-1-methyl-1*H*-pyrazol-5-yl)-4-methoxy-2-(trifluoromethyl)benzothiazole-7-carboxamide



C15 H10 F3 N5 O2 S; Mol wt: 381.3370

ACTION – An inhibitor of TNF production and phosphodiesterase type 4 (PDE4) activity, potentially useful for the treatment of inflammatory and autoimmune diseases, particularly asthma, chronic obstructive pulmonary disease (COPD) and chronic bronchitis. Another specifically claimed benzothiazole derivative is:



308907: C₁₇ H₁₅ N₅ O₂ S

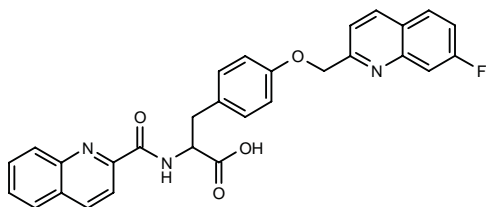
SOURCE – Darwin Discovery.

REFERENCES

1. Dyke, H.J. et al. (Darwin Discovery Ltd.) *Benzthiazoles as TNF and PDE-IV inhibitors*. US 6313116, WO 0158897.

309143

4-*O*-(7-Fluoroquinolin-2-ylmethyl)-*N*-(quinolin-2-ylcarbonyl)-DL-tyrosine



C₂₉ H₂₂ F N₃ O₄; Mol wt: 495.5078

ACTION – Leukotriene antagonist found to inhibit the binding of [³H]-LTD₄ to receptors in guinea pig lung membranes with an IC₅₀ of 7.9 nM, and to exhibit a dose-dependent inhibitory effect against LTD₄-induced contractions of guinea pig tracheal strips. *In vivo*, compound was able to completely prevent ovalbumin-induced bronchoconstriction in guinea pigs following oral administration (0.3 mg/kg). In addition, it gave an LD₅₀ of > 50 mg/kg i.v. and > 300 mg/kg p.o. in mice. Potentially useful for the treatment of allergic or inflammatory diseases of the respiratory tract including bronchial asthma, obstructive lung diseases, hay fever and allergic rhinitis, as well as for the treatment of irritative eye conditions, ulcerative colitis, Crohn's disease and food allergies.

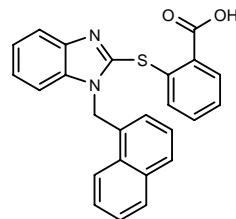
SOURCE – Rotta.

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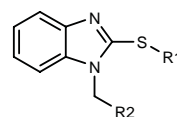
309240

2-[1-(Naphthalen-1-ylmethyl)-1*H*-benzimidazol-2-ylsulfanyl]benzoic acid



C₂₅ H₁₈ N₂ O₂ S; Mol wt: 410.4952

ACTION – Human mast cell chymase inhibitor (IC₅₀ in the range 0.1-1 μM against activated human recombinant enzyme), with potential in the treatment of inflammatory, allergic, respiratory, cardiovascular and bone and cartilage disorders. A representative compound from a series of substituted benzimidazole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
309243	2-CO ₂ H-Ph	Ph	C ₂₁ H ₁₆ N ₂ O ₂ S
309246	6-CO ₂ H-2-Pyr	1-Naph	C ₂₄ H ₁₇ N ₃ O ₂ S

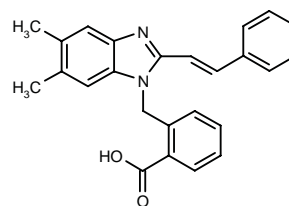
SOURCE – Teijin.

REFERENCES

1. Matsumoto, Y. and Tsuchiya, N. (Teijin Ltd.) *Benzimidazole derivs*. JP 2001199983.

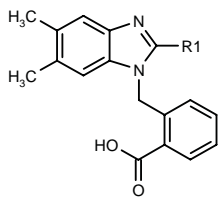
309248

2-[5,6-Dimethyl-2-(2-phenylvinyl)-1*H*-benzimidazol-1-ylmethyl]benzoic acid



C₂₅ H₂₂ N₂ O₂; Mol wt: 382.4608

ACTION – Human mast cell chymase inhibitor (IC₅₀ in the range 1-10 μM against activated human recombinant enzyme), with potential in the treatment of inflammatory, allergic, respiratory, cardiovascular and bone and cartilage disorders. A representative compound from a series of substituted benzimidazole derivatives, wherein the following are also included:



Compound	R1	Formula
309249	(CH2)4Ph	C ₂₇ H ₂₈ N ₂ O ₂
309250	Ph	C ₂₃ H ₂₀ N ₂ O ₂

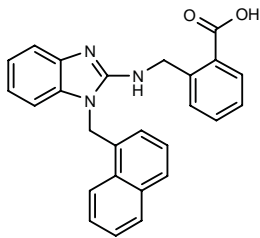
SOURCE – Teijin.

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1. Matsumoto, Y. and Saito, H. (Teijin Ltd.) *Benzimidazole derivs.* JP 2001199967.

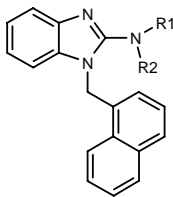
309254

2-[1-(Naphthalen-1-ylmethyl)-1H-benzimidazol-2-ylaminomethyl]benzoic acid



C26 H21 N3 O2; Mol wt: 407.4709

ACTION – Human mast cell chymase inhibitor (IC₅₀ in the range 0.1-1 μM against activated human recombinant enzyme), with potential in the treatment of inflammatory, allergic, respiratory, cardiovascular and bone and cartilage disorders. A representative compound from a series of aminobenzimidazole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
309256	Me	4-CO2H-PhCO	C ₂₇ H ₂₁ N ₃ O ₃
309259	Me	2-CO2H-PhSO2	C ₂₆ H ₂₁ N ₃ O ₄ S
309260	H	4-CO2H-Ph	C ₂₅ H ₁₉ N ₃ O ₂

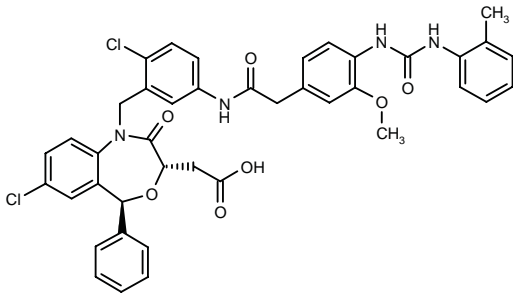
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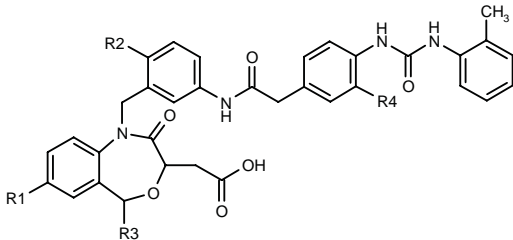
309327

(+)-*trans*-2-[7-Chloro-1-[2-chloro-5-[2-[3-methoxy-4-[3-(2-methylphenyl)ureido]phenyl]acetamido]benzyl]-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid

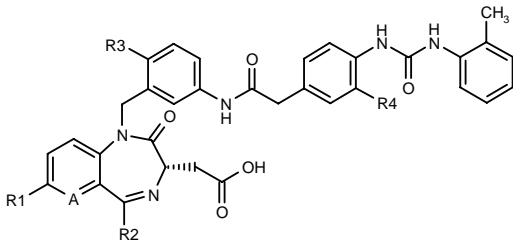


C41 H36 Cl2 N4 O7; Mol wt: 767.6624

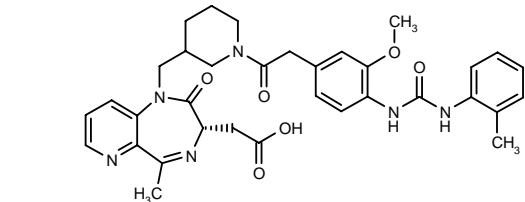
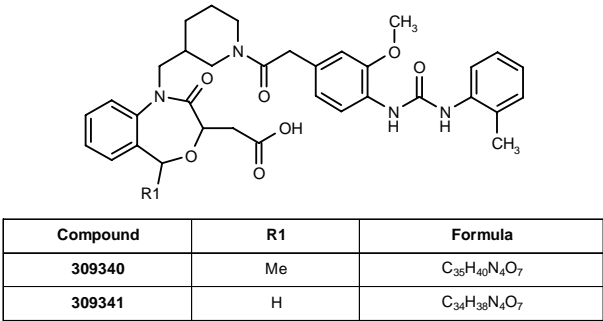
ACTION – VLA-4 antagonist with excellent oral bioavailability, proven to inhibit the adhesion of HL-60 cells to human VCAM-1-expressing CHO cells with an IC₅₀ of 0.072 μM. Potentially useful for the treatment of rheumatoid arthritis, nephritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory neurological disorders, asthma, allergy, multiple sclerosis, cardiovascular diseases, arteriosclerosis, diabetes, cancer and organ transplant rejection. Other exemplified azepine derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
309330	Cl	H	Ph	H	trans	C ₄₀ H ₃₅ ClN ₄ O ₆
309331	Cl	Cl	Ph	OMe	(±)-trans	C ₄₁ H ₃₆ Cl ₂ N ₄ O ₇
309332	Cl	Cl	Ph	OMe	(-)-trans	C ₄₁ H ₃₆ Cl ₂ N ₄ O ₇
309333	H	Cl	Me	OMe		C ₃₆ H ₃₅ ClN ₄ O ₇



Compound	R1	R2	R3	R4	A	Formula
309334	Cl	Ph	H	H	CH	C ₄₀ H ₃₄ ClN ₆ O ₅
309336	H	Me	Cl	OMe	N	C ₃₅ H ₃₃ ClN ₆ O ₆



309343: C34 H38 N6 O6

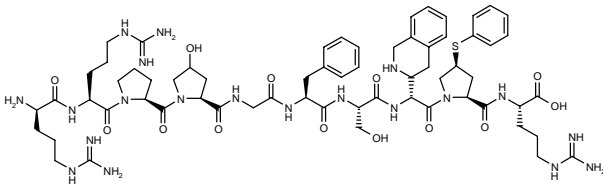
SOURCE – Kaken.

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309685

D-Arginyl-L-arginyl-L-prolyl-4-hydroxy-L-prolyl-glycyl-L-phenylalanyl-L-seryl-2-(1,2,3,4-tetrahydroisoquinolin-3-yl)-D-glycyl-4(S)-(phenylsulfanyl)-L-prolyl-L-arginine



C64 H92 N20 O13 S; Mol wt: 1381.6240

ACTION – Bradykinin receptor antagonist, as demonstrated in a binding assay by a K_i value of 0.06 ± 0.01 mM for inhibition of [3 H]-bradykinin binding in guinea pig terminal ileum preparations and in a functional assay by a pA_2 value of 7.95 for inhibition of bradykinin-induced contractions of guinea pig ileal longitudinal smooth muscle. Potentially useful in the treatment of a broad range of disorders including inflammatory disorders, asthma, allergies, septic shock and local pain from burns, wounds and trauma. A representative compound from a series of bradykinin-type peptides.

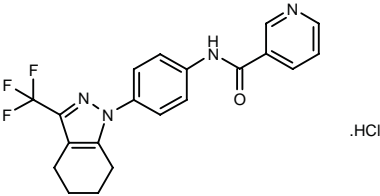
SOURCE – Scios.

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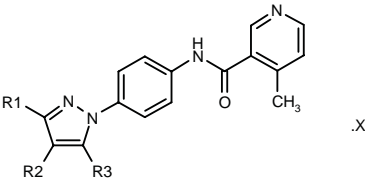
309688

N-[4-[3-(Trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl]pyridine-3-carboxamide hydrochloride

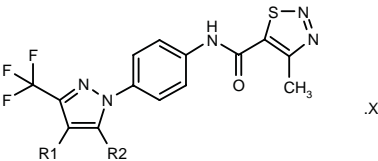


C20 H17 F3 N4 O . HCl; Mol wt: 422.8362

ACTION – An inhibitor of calcium (Ca^{2+}) release-activated calcium channels (CRACC) and IL-2 production, potentially useful for the treatment of inflammatory and autoimmune diseases including bronchial asthma, psoriasis, atopic dermatitis, peptic ulcer, nephritis, hepatitis, pancreatitis, rheumatoid arthritis, osteoarthritis and transplant rejection, as well as proliferative or progressive diseases such as cancer, arteriosclerosis, multiple sclerosis and fibrosis. Other exemplified compounds from this series of condensed pyrazole derivatives include the following:



Compound	R1	R2	R3	X	Formula
309689	CF3	-CH2N(Me)CH2CH2-		dioxalate	C ₂₁ H ₂₀ F ₃ N ₅ O.2C ₂ H ₂ O ₄
309691		-(CH2)4-	CF3	HCl	C ₂₁ H ₁₉ F ₃ N ₄ O.HCl
309692	CF3	-(CH2)3-		HCl	C ₂₀ H ₁₇ F ₃ N ₄ O.HCl
309694		-(CH2)3-	CF3	HCl	C ₂₀ H ₁₇ F ₃ N ₄ O.HCl
309695	CF3	-CH2NHCH2CH2-		2HCl	C ₂₀ H ₁₈ F ₃ N ₅ O.2HCl



Compound	R1,R2	X	Formula
309690	-CH2NHCH2CH2-	HCl H2O	C ₁₇ H ₁₅ F ₃ N ₆ OS.HCl.H2O
309693	-(CH2)4-		C ₁₈ H ₁₆ F ₃ N ₅ OS

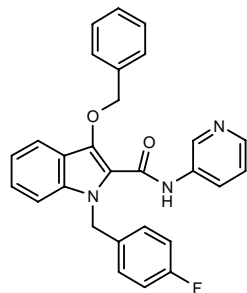
SOURCE – Yamanouchi.

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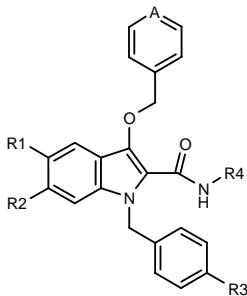
309856

3-(Benzyloxy)-1-(4-fluorobenzyl)-N-(3-pyridyl)-1*H*-indole-2-carboxamide



C28 H22 F N3 O2; Mol wt: 451.4988

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful for the treatment of asthma, muscular spasm, cystic fibrosis, chronic bronchitis, psoriasis and other proliferative skin diseases, septic shock, ulcerative colitis, Crohn’s disease, brain and myocardial reperfusion injury, arthritis, osteoporosis, atopic dermatitis, respiratory distress syndrome, diabetes, allergic rhinitis, arterial restenosis and atherosclerosis, among other PDE4-mediated conditions. Other exemplified compounds are:



Compound	R1	R2	R3	R4	A	Formula
309857	H	H	F	3-MeSO2-Ph	CH	C ₃₀ H ₂₆ FN ₂ O ₄ S
309858	H	H	F	4-Pyr-CH2	CH	C ₂₉ H ₂₄ FN ₃ O ₂
309859	H	H	CH(Me)2OH	3-Pyr	CH	C ₃₁ H ₂₉ N ₃ O ₃
309861	H	H	t-Bu	3-Pyr	CH	C ₃₂ H ₃₁ N ₃ O ₂
309862	H	H	OCHF2	3-Pyr	CH	C ₂₉ H ₂₃ F ₂ N ₃ O ₃
309863	H	H	F	3-Pyr	N	C ₂₇ H ₂₁ FN ₄ O ₂
309864	Br	H	F	3-Pyr	CH	C ₂₈ H ₂₁ BrFN ₃ O ₂
309865	CO2H	H	F	3-Pyr	CH	C ₂₉ H ₂₂ FN ₃ O ₄
309866	H	CH(Me)2OH	F	3-Pyr	CH	C ₃₁ H ₂₈ FN ₃ O ₃

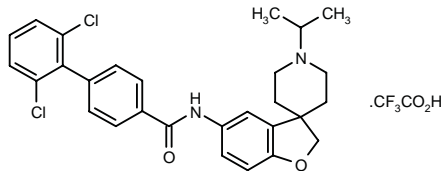
SOURCE – Merck Frosst.

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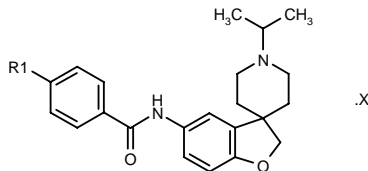
309912

2',6'-Dichloro-N-(1'-isopropyl-2,3-dihydrospiro[benzofuran-3,4'-piperidin]-5-yl)biphenyl-4-carboxamide trifluoroacetate



C28 H28 Cl2 N2 O2 . C2 H F3 O2; Mol wt: 609.4691

ACTION – Chemokine CCR5 receptor modulator, potentially useful for the treatment of chronic obstructive pulmonary disease (COPD), asthma, atopic disorders, rheumatoid arthritis, sarcoidosis, idiopathic pulmonary fibrosis, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, transplant rejection, inflammatory bowel disease and HIV infection. Other specifically claimed compounds are:



Compound	R1	X	Formula
309914	cyclohexyl		C ₂₈ H ₃₆ N ₂ O ₂
309916	2-Cl-Ph	CF3CO2H	C ₂₈ H ₂₉ ClN ₂ O ₂ ·C ₂ HF ₃ O ₂

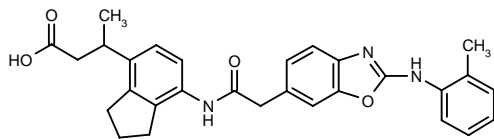
SOURCE – GlaxoSmithKline.

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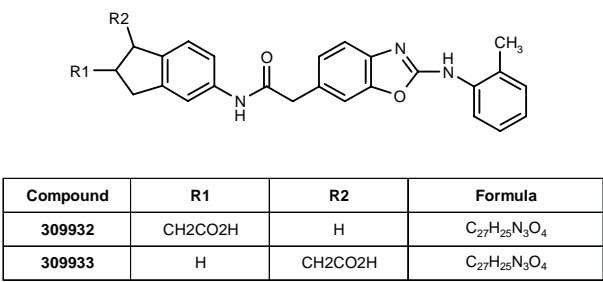
309930

3-[7-[2-[2-(2-Methylphenylamino)benzoxazol-6-yl]acetamido]indan-4-yl]butyric acid



C29 H29 N3 O4; Mol wt: 483.5651

ACTION – An inhibitor of the interaction of VCAM-1 and fibronectin with the integrin receptor VLA-4 ($\alpha_4\beta_1$), with potential in the treatment of diseases mediated by $\alpha_4\beta_1$ -regulated cell adhesion such as asthma and inflammatory diseases. Other substituted indane derivatives include the following:



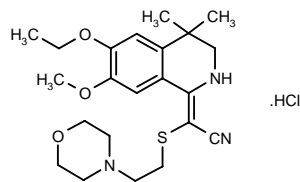
SOURCE – Aventis Pharma.

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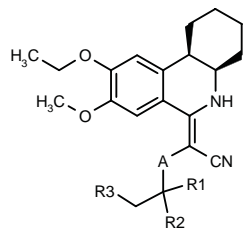
309940

2-(6-Ethoxy-7-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylidene)-2-[2-(4-morpholinyl)ethylsulfanyl]-acetonitrile hydrochloride

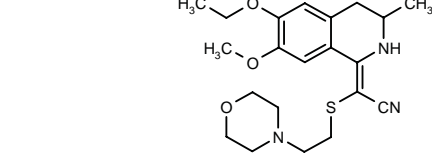


C22 H31 N3 O3 S . HCl; Mol wt: 454.0318

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 2.7 nM) with high selectivity over PDE2, PDE3 and PDE5 subtypes. Potentially useful for the treatment of asthma, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis. Other specifically claimed isoquinoline derivatives include the following:



Compound	R1	R2	R3	A	Formula
309942	H	H	4-morpholinyl	S	C ₂₄ H ₃₃ N ₃ O ₃ S
309943	H	H	4-morpholinyl	S	C ₂₄ H ₃₃ N ₃ O ₃ S
309945	H	H	4-morpholinyl	S	C ₂₄ H ₃₃ N ₃ O ₃ S
309947	Me	H	4-morpholinyl	S	C ₂₅ H ₃₅ N ₃ O ₃ S
309948	Me	Me	4-morpholinyl	S	C ₂₆ H ₃₇ N ₃ O ₃ S
309949	H	H	1-pyrrolidinyl	S	C ₂₄ H ₃₃ N ₃ O ₂ S
309951	H	H	1-Pip	S	C ₂₅ H ₃₅ N ₃ O ₂ S
309952	H	H	1-pyrrolidinyl	O	C ₂₄ H ₃₃ N ₃ O ₃
309953	H	H	1-Pip	O	C ₂₅ H ₃₅ N ₃ O ₃
309954	H	H	4-morpholinyl	O	C ₂₄ H ₃₃ N ₃ O ₄



309941: C21 H29 N3 O3 S

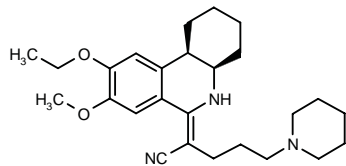
SOURCE – Sanofi-Synthélabo.

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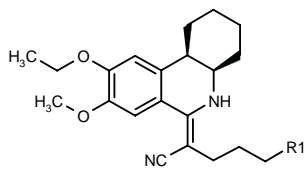
309956

(±)-cis-2-(9-Ethoxy-8-methoxy-1,2,3,4,4a,5,6,10b-octa-hydrophenanthridin-6-ylidene)-5-(1-piperidinyl)-pentanenitrile



C26 H37 N3 O2; Mol wt: 423.5973

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 6 nM) with high selectivity over PDE2, PDE3 and PDE5 subtypes. Potentially useful for the treatment of asthma, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis. Other specifically claimed isoquinoline derivatives include the following:



Compound	R1	Isomer	Formula
309958	1-pyrrolidinyl	racemic	C ₂₅ H ₃₅ N ₃ O ₂
309959	4-morpholinyl	racemic	C ₂₅ H ₃₅ N ₃ O ₃
309960	1-pyrrolidinyl	(-)	C ₂₅ H ₃₅ N ₃ O ₂

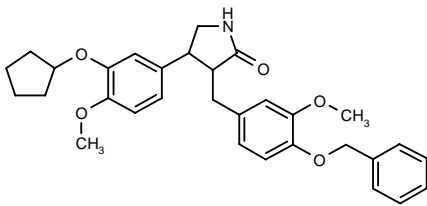
SOURCE – Sanofi-Synthélabo.

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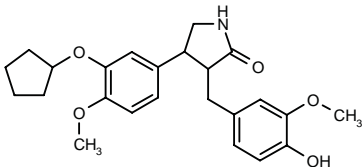
310026

3-[4-(Benzyloxy)-3-methoxybenzyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidin-2-one

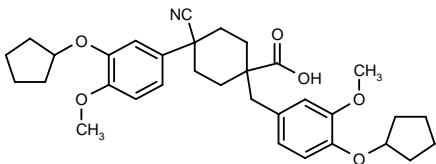


C31 H35 N O5; Mol wt: 501.6195

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC_{50} = 0.40 μ M) with reduced emetogenic properties. Potentially useful for the treatment of inflammatory and autoimmune diseases including asthma, arthritis, multiple sclerosis, pulmonary sarcoidosis, ocular inflammation or allergy, Crohn’s disease, ulcerative colitis, psoriasis, dermatitis, chronic obstructive pulmonary disease (COPD), bronchitis, emphysema and acute respiratory distress syndrome (ARDS). The use of this compound for the treatment of transplant rejection, cancer, depression, memory and learning disorders, HIV infection, cystic fibrosis and parasitic infections is also claimed. Other benzylated compounds are:



310027: C24 H29 N O5



310029: C33 H41 N O6

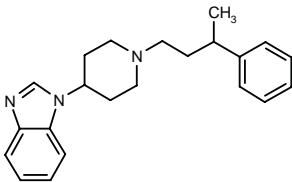
SOURCE – InflaZyme.

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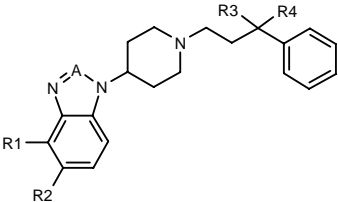
310100

1-[1-(3-Phenylbutyl)piperidin-4-yl]-1*H*-benzimidazole



C22 H27 N3; Mol wt: 333.4763

ACTION – Chemokine CCR5 receptor modulator shown to inhibit the binding of MIP-1 α to membranes of CHO cells expressing CCR5 receptors. Potentially useful for the treatment of asthma, transplant rejection, rheumatoid arthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, ulcerative colitis, multiple sclerosis, glomerulonephritis, chronic obstructive pulmonary disease (COPD), cerebral malaria, HIV infection and AIDS. Other exemplified compounds are:



Compound	R1	R2	R3	R4	A	Formula
310101	H	H	Ph	H	CH	C ₂₇ H ₂₉ N ₃
310102	H	F	Me	H	CH	C ₂₂ H ₂₆ FN ₃
310103	F	H	Me	H	CH	C ₂₂ H ₂₆ FN ₃
310104	H	H	Ph	H	N	C ₂₆ H ₂₈ N ₄
310105	H	H	CN	Ph	CH	C ₂₈ H ₂₈ N ₄
310106	H	SO ₂ Me	(S)-Me	H	CH	C ₂₃ H ₂₉ N ₃ O ₂ S
310108	H	SO ₂ Me	Ph	H	CH	C ₂₈ H ₃₁ N ₃ O ₂ S
310109	H	CN	Ph	H	CH	C ₂₈ H ₂₈ N ₄

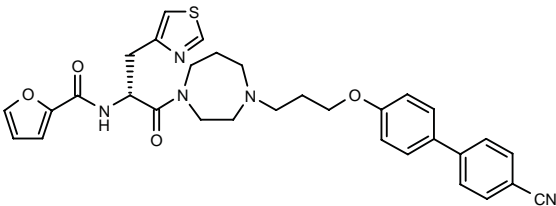
SOURCE – AstraZeneca.

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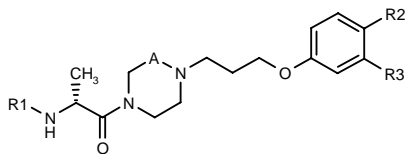
310131

N-[2-[4-[3-(4'-Cyanobiphenyl-4-yloxy)propyl]perhydro-1,4-diazepin-1-yl]-2-oxo-1(*R*)-(thiazol-4-ylmethyl)ethyl]furan-2-carboxamide



C32 H33 N5 O4 S; Mol wt: 583.7097

ACTION – Histamine H₃ receptor antagonist with a K_i of 0.208 nM against H₃ receptors in rat cortical membranes. Potentially useful for the treatment of asthma, cardiovascular disorders, gastrointestinal disorders, inflammation and sleep disorders, and as a sedative, anticonvulsant and antidepressant. Other exemplified cyclic and bicyclic diamino compounds include the following:



Compound	R1	R2	R3	A	Formula
310132	2-furyl-CO	cyclopropyl-CO	H	-CH2-	C ₂₅ H ₃₁ N ₃ O ₅
310134	H-D-Pro-	cyclopropyl-CO	H	-CH2-	C ₂₅ H ₃₆ N ₄ O ₄
310135	H	cyclopropyl-CO	H	-CH2-	C ₂₀ H ₂₉ N ₃ O ₃
310136	2-furyl-CO	5-(i-BuCH2)- -1,2,4-oxadiazol-3-yl	F	-(CH2)2-	C ₂₉ H ₃₈ FN ₅ O ₅
310137	4-F-PhCO	5-(cyclophenyl-CH2)- -1,2,4-oxadiazol-3-yl	F	-CH2-	C ₃₁ H ₃₇ F ₂ N ₅ O ₄

SOURCE – Abbott.

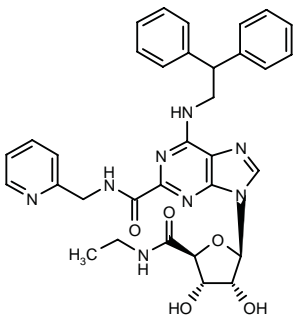
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AGENTS FOR RESPIRATORY DISTRESS SYNDROME

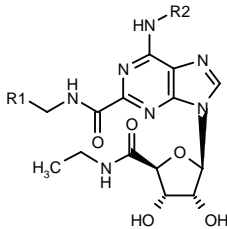
309012

1-Deoxy-1-[N⁶-(2,2-diphenylethyl)-2-[N-(pyridin-2-ylmethyl)carbamoyl]adenin-9-yl]-N-ethyl-β-D-ribofuranuronamide



C33 H34 N8 O5; Mol wt: 622.6826

ACTION – Selective adenosine A_{2A} receptor agonist potentially useful as an antiinflammatory agent, particularly in the treatment of respiratory diseases including adult respiratory distress syndrome (ARDS), bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, asthma, emphysema, bronchiec-tasis, chronic sinusitis and rhinitis. Other specifically claimed purine derivatives are:



Compound	R1	R2	Formula
309013	CH2N(Me)2	CH2CH(Ph)2	C ₃₁ H ₃₈ N ₈ O ₅
309014	1-Pip-CH2	CH(Et)2	C ₂₅ H ₄₀ N ₈ O ₅
309015	4-Pip	CH2CH(Ph)2	C ₃₃ H ₄₀ N ₈ O ₅
309016	CH2CH2N(Me)SO2Ph	CH2CH(Ph)2	C ₃₇ H ₄₂ N ₈ O ₇ S
309017	CH2CH2NHMe	CH2CH(Ph)2	C ₃₁ H ₃₈ N ₈ O ₅
309018	CH2CH2N(Me)2	CH2CH(Ph)2	C ₃₂ H ₄₀ N ₈ O ₅
309019	4-Me-1-Pip-CH2	CH2CH(Ph)2	C ₃₅ H ₄₄ N ₈ O ₅
309020	1-Pip-CH2	cyclohexyl	C ₂₆ H ₄₀ N ₈ O ₅

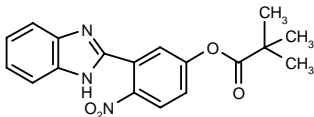
SOURCE – Pfizer.

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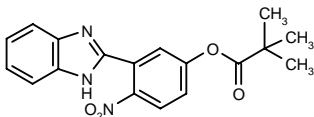
309612

2,2-Dimethylpropionic acid 3-(1*H*-benzimidazol-2-yl)-4-nitrophenyl ester



C18 H17 N3 O4; Mol wt: 339.3493

ACTION – Elastase inhibitor (IC₅₀ = 59.0 nM) with low oral toxicity (LD₅₀ > 500 mg/kg in mice). Other exemplified 2,2-dimethylpropionic acid esters include the following:



Compound	R1	R2	R3	R4	Formula
309613	H	H	1-Pip-CH2CH2	F	C ₂₅ H ₃₀ FN ₃ O ₂
309614	H	H	CH2CH2N(Me)2	H	C ₂₂ H ₂₇ N ₃ O ₂
309615	NO2	H	H	H	C ₁₈ H ₁₇ N ₃ O ₄
309616	Me	Me	1-Pip-CH2CH2	H	C ₂₇ H ₃₅ N ₃ O ₂

SOURCE – Cermol.

REFERENCES

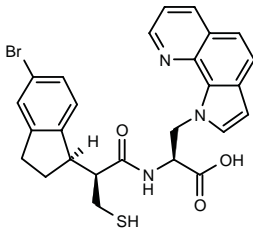
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

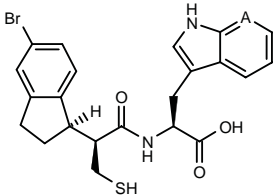
308882

N-[2(*S*)-[5-Bromo-2,3-dihydro-1*H*-inden-1(*R*)-yl]-3-sulfanylpropionyl]-3-(1*H*-pyrrolo[3,2-*h*]quinolin-1-yl)-L-alanine



C26 H24 Br N3 O3 S; Mol wt: 538.4636

ACTION – An inhibitor of neutral endopeptidase (NEP; K_i = 10.2 nM), endothelin-converting enzyme (ECE; K_i = 21.2 nM) and/or angiotensin-converting enzyme (ACE; K_i = 3.7 nM), potentially useful for the treatment of cardiovascular disorders including arterial hypertension, myocardial ischemia, angina pectoris, cardiac insufficiency, atherosclerosis, renal insufficiency, stroke, etc. Other exemplified amino acid derivatives are:



Compound	A	Formula
308884	N	C ₂₂ H ₂₂ BrN ₃ O ₃ S
308885	CH	C ₂₃ H ₂₃ BrN ₃ O ₃ S

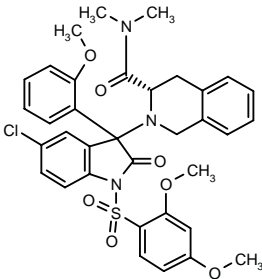
SOURCES – ADIR; INSERM, Paris Cedex (FR).

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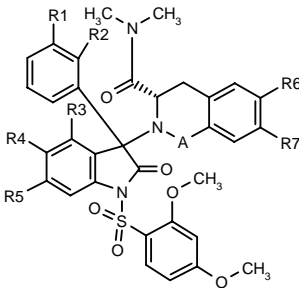
309879

(–)-2-[5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-*N,N*-dimethyl-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxamide



C35 H34 Cl N3 O7 S; Mol wt: 676.1866

ACTION – Agent with affinity for arginine-vasopressin (AVP) receptors, particularly selective for the V_{1b} or both the V_{1b} and V_{1a} receptor subtypes. Potentially useful for the treatment of cardiovascular disorders such as hypertension, CNS disorders including stress, anxiety, depression, obsessive–compulsive disorders and panic, gastric and renal disorders, small cell lung cancer, obesity, type 2 diabetes, insulin resistance, hypertriglyceridemia, atherosclerosis, Cushing’s syndrome and chronic stress-related disorders. Other specifically claimed 3,4-dihydro-2*H*-indol-2-one compounds include the following:



Compound	R1	R2	R3	R4	R5	R6=R7	A	Formula
309880	H	OMe	H	Cl	H	H	bond	C ₃₄ H ₃₂ ClN ₃ O ₇ S
309881	H	OMe	H	Cl	Cl	H	-CH2-	C ₃₅ H ₃₃ Cl ₂ N ₃ O ₇ S
309882	H	OMe	H	Cl	H	OMe	-CH2-	C ₃₇ H ₃₅ ClN ₃ O ₉ S
309883	OMe	OMe	H	Cl	H	H	-CH2-	C ₃₆ H ₃₆ ClN ₃ O ₈ S
309884	-OCH2O-	H	Cl	H	H	H	-CH2-	C ₃₅ H ₃₂ ClN ₃ O ₈ S
309885	H	Cl	H	Cl	OMe	H	-CH2-	C ₃₅ H ₃₃ Cl ₂ N ₃ O ₇ S
309888	H	OMe	Cl	Me	H	H	-CH2-	C ₃₆ H ₃₆ ClN ₃ O ₇ S

SOURCE – Sanofi-Synthélabo.

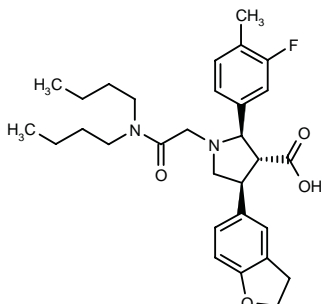
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A-306552

310660

1-(*N,N*-Dibutylcarbamoylmethyl)-4(*S*)-(2,3-dihydrobenzofuran-5-yl)-2(*R*)-(3-fluoro-4-methylphenyl)pyrrolidine-3(*R*)-carboxylic acid



C30 H39 F N2 O4; Mol wt: 510.6461

ACTION – Potent, orally available endothelin ET_A receptor antagonist with high affinity for ET_A over ET_B receptors (IC₅₀ = 0.16 and 6200 nM, respectively). Compound exhibited a favorable pharmacokinetic profile in rats after oral administration, with an oral bioavailability > 70% and a half-life of 4.7 h. Potentially useful as an antihypertensive agent.

SOURCE – Abbott.

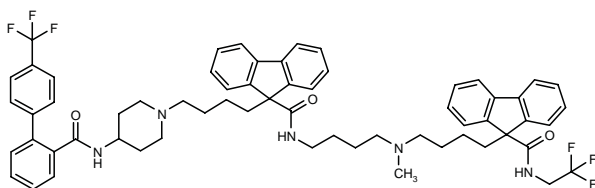
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

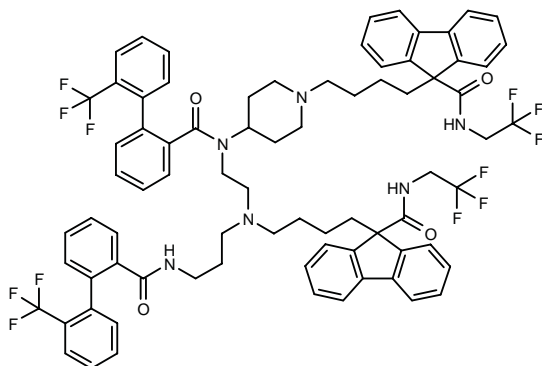
308690

9-[4-[*N*-Methyl-*N*-[4-[9-[4-[4-[4'-(trifluoromethyl)biphenyl-2-ylcarboxamido]piperidin-1-yl]butyl]-9*H*-fluoren-9-ylcarboxamido]butyl]amino]butyl]-*N*-(2,2,2-trifluoroethyl)-9*H*-fluorene-9-carboxamide

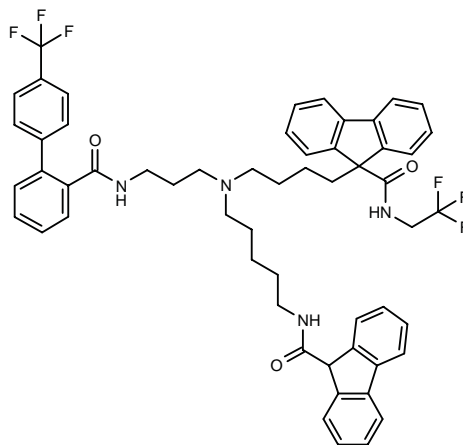


C62 H65 F6 N5 O3; Mol wt: 1042.2150

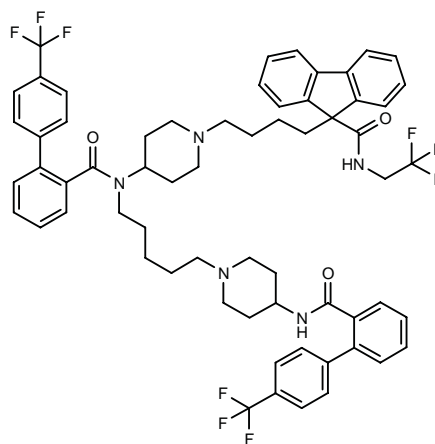
ACTION – A multibinding-type inhibitor of microsomal triglyceride transferase protein (MTP), reported to be effective as a lipid-, cholesterol- and/or triglyceride-lowering agent, and thus expected to be useful for the treatment of atherosclerosis.



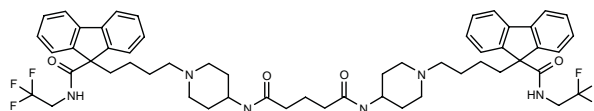
308714: C78 H74 F12 N6 O4



308715: C56 H54 F6 N4 O3



308716: C63 H64 F9 N5 O3



308717: C55 H64 F6 N6 O4

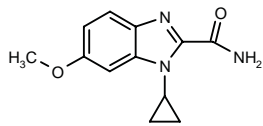
SOURCE – Advanced Medicine.

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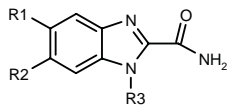
308848

1-Cyclopropyl-6-methoxy-1*H*-benzimidazole-2-carboxamide



C12 H13 N3 O2; Mol wt: 231.2537

ACTION – Agent for the treatment of ischemia–reperfusion injury with the ability to block the adhesion of neutrophils to endothelium. Potentially useful for the treatment of conditions involving ischemia–reperfusion injury including myocardial infarction, coronary artery bypass grafting, angioplasty, angina, stroke, inflammatory bowel disease, ulcerative colitis, adult respiratory distress syndrome, asthma, acute renal failure and rheumatoid arthritis, among others. Other exemplified benzimidazole-2-carboxamides include the following:



Compound	R1	R2	R3	Formula
308849	H	OMe	cyclobutyl	C ₁₃ H ₁₅ N ₃ O ₂
308850	H	OMe	cyclopentyl	C ₁₄ H ₁₇ N ₃ O ₂
308851	H	OMe	cyclohexyl	C ₁₅ H ₁₉ N ₃ O ₂
308852	H	OMe	i-Pr	C ₁₂ H ₁₅ N ₃ O ₂
308853	H	OMe	i-Bu	C ₁₃ H ₁₇ N ₃ O ₂
308854	H	OMe	i-BuCH2	C ₁₄ H ₁₉ N ₃ O ₂
308855	H	OMe	Pr	C ₁₂ H ₁₅ N ₃ O ₂
308856	H	OMe	Bu	C ₁₃ H ₁₇ N ₃ O ₂
308857	H	OMe	CH2CH2OMe	C ₁₂ H ₁₅ N ₃ O ₃
308858	H	NH2	i-Bu	C ₁₂ H ₁₆ N ₄ O
308861	OMe	H	i-Bu	C ₁₃ H ₁₇ N ₃ O ₂
308863	H	4-MeO-PhCH2NH	i-Bu	C ₂₀ H ₂₄ N ₄ O ₂
308865	H	NHCOCH(NH2)CH2Ph	i-Bu	C ₂₁ H ₂₅ N ₅ O ₂

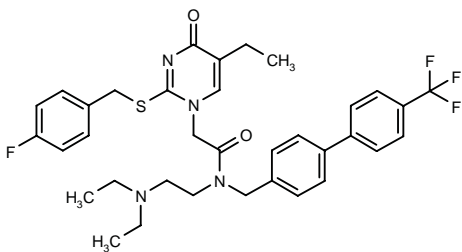
SOURCE – Procter & Gamble.

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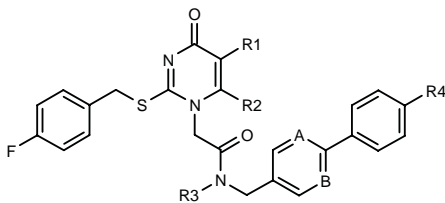
309068

N-[2-(Diethylamino)ethyl]-2-[5-ethyl-2-(4-fluorobenzyl-sulfanyl)-4-oxo-1,4-dihydropyrimidin-1-yl]-*N*-[4'-(trifluoromethyl)biphenyl-4-ylmethyl]acetamide



C35 H38 F4 N4 O2 S; Mol wt: 654.7692

ACTION – Inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) with potential in the primary and secondary prevention of acute coronary events caused by atherosclerosis. Other exemplified pyrimidin-4-one derivatives include the following:



Compound	R1	R2	R3	R4	A	B	Formula
309069	Me	H	Me	CF3	N	CH	C ₂₈ H ₂₄ F ₄ N ₄ O ₂ S
309070	Et	H	CH2CH2N(Et)2	Cl	N	N	C ₃₂ H ₃₆ ClFN ₆ O ₂ S
309071	CH2CH2OH	H	CH2CH2N(Et)2	Cl	CH	CH	C ₃₄ H ₃₆ ClFN ₄ O ₃ S
309072	OMe	H	CH2CH2N(Et)2	CF3	N	CH	C ₃₃ H ₃₅ F ₄ N ₅ O ₃ S
309073	-(CH2)3-		Me	CF3	CH	CH	C ₃₁ H ₂₇ F ₄ N ₃ O ₂ S
309074	-(CH2)3-		1-Me-4-Pip	CF3	CH	CH	C ₃₆ H ₃₆ F ₄ N ₄ O ₂ S
309075	-(CH2)3-		CH2CH2NHEt	CF3	CH	CH	C ₃₄ H ₃₄ F ₄ N ₄ O ₂ S

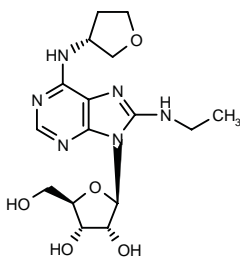
SOURCE – GlaxoSmithKline.

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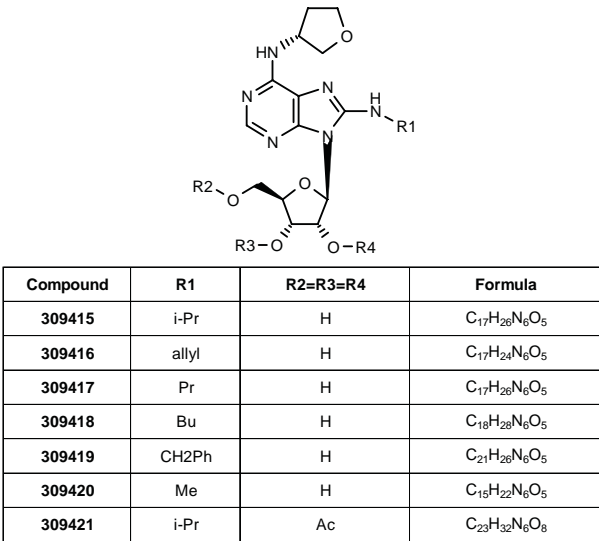
309414

8-(Ethylamino)-*N*⁶-[tetrahydrofuran-3(*R*)-yl]adenosine



C16 H24 N6 O5; Mol wt: 380.4026

ACTION – A selective partial or full adenosine A₁ receptor agonist with K_i values of 171 and 137 nM against A₁ receptors in DDT1 cells and pig striatum, respectively. Potentially useful for modifying cardiac activity, as well as for modifying adipocyte function and treating CNS disorders, diabetes and obesity. Other specifically claimed *N*⁶-heterocyclic 8-modified adenosine analogues are:



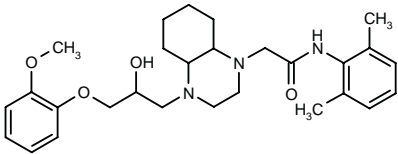
SOURCE – CV Therapeutics.

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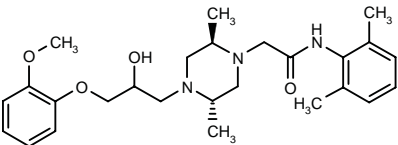
309499

N-(2,6-Dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]perhydroquinoxalin-1-yl]acetamide



C28 H39 N3 O4; Mol wt: 481.6331

ACTION – Partial fatty acid oxidation inhibitor, as demonstrated in *in vitro* assays in rat heart mitochondria using palmitoyl CoA or palmitoyl carnitine as substrate. Potentially useful for protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, treating shock conditions, preserving donor tissue and organs used in transplants, and treating cardiovascular diseases such as atrial and ventricular arrhythmias, angina, congestive heart disease and myocardial infarction. Another compound from this series of substituted piperazine derivatives is:



309501: C26 H37 N3 O4

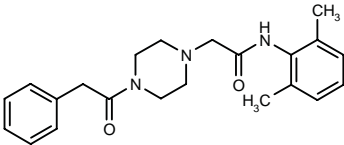
SOURCE – CV Therapeutics.

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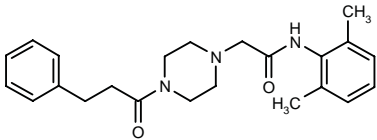
309502

N-(2,6-Dimethylphenyl)-2-[4-(2-phenylacetyl)piperazin-1-yl]acetamide



C22 H27 N3 O2; Mol wt: 365.4743

ACTION – Partial fatty acid oxidation inhibitor, as demonstrated in *in vitro* assays in rat heart mitochondria using palmitoyl CoA or palmitoyl carnitine as substrate. Potentially useful for protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, treating shock conditions, preserving donor tissue and organs used in transplants, and treating cardiovascular diseases such as atrial and ventricular arrhythmias, angina, congestive heart disease and myocardial infarction. Another compound from this series of substituted piperazine derivatives is:



309503: C23 H29 N3 O2

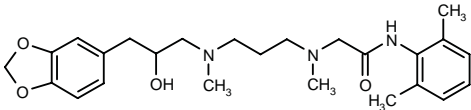
SOURCE – CV Therapeutics.

REFERENCES

1. Blackburn, B. et al. (CV Therapeutics, Inc.) *Substd. piperazine cpds.* WO 0162749.

309504

2-[*N*-[3-[*N*-[3-(1,3-Benzodioxol-5-yl)-2-hydroxypropyl]-*N*-methylamino]propyl]-*N*-methylamino]-*N*-(2,6-dimethylphenyl)acetamide



C25 H35 N3 O4; Mol wt: 441.5685

ACTION – Partial fatty acid oxidation inhibitor, as demonstrated in *in vitro* assays in rat heart mitochondria using palmitoyl CoA or palmitoyl carnitine as substrate. Potentially useful for protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, treating shock conditions, preserving donor tissue and organs used in transplants, and treating cardiovascular diseases such as atrial and ventricular arrhythmias, angina, congestive heart disease and myocardial infarction. A representative compound from a series of substituted alkylene diamine derivatives.

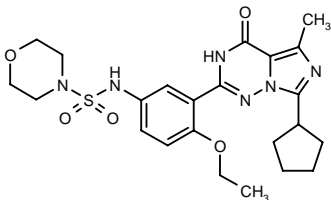
SOURCE – CV Therapeutics.

REFERENCES

1. Elzein, E. et al. (CV Therapeutics, Inc.) *Substd. alkylene diamine cpds.* WO 0162711.

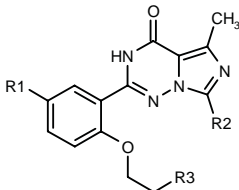
309798

N-[3-(7-Cyclopentyl-5-methyl-4-oxo-3,4-dihydroimidazo-[5,1- η][1,2,4]triazin-2-yl)-4-ethoxyphenyl]morpholine-4-sulfonamide



C23 H30 N6 O5 S; Mol wt: 502.5930

ACTION – An inhibitor of cGMP-phosphodiesterases with potential for the treatment of cardiovascular and cerebrovascular disorders, as well as diseases of the urogenital tract. Other specifically claimed compounds within this series of substituted imidazotriazinone derivatives include the following:



Compound	R1	R2	R3	Formula
309799	4-Me-1-Piz-SO2NH	cyclopentyl	Me	C ₂₅ H ₃₆ N ₇ O ₄ S
309800	1-Et-4-Piz-SO2NH	CH(Et)2	H	C ₂₅ H ₃₇ N ₇ O ₄ S
309801	4-morpholinyl-CONH	cyclopentyl	H	C ₂₄ H ₃₀ N ₆ O ₄
309802	4-morpholinyl-CONH	CH(Et)2	H	C ₂₄ H ₃₂ N ₆ O ₄
309803	CH2N(Me)CH2CH2OH	Pr	H	C ₂₁ H ₂₉ N ₅ O ₃
309804	4-Me-1-Piz-CH2	C(Me)2Pr	H	C ₂₆ H ₃₈ N ₆ O ₂
309805	4-Me-1-Piz-CH2CO	Pr	H	C ₂₄ H ₃₂ N ₆ O ₃
309806	4-Et-1-Piz-CO	Pr	H	C ₂₄ H ₃₂ N ₆ O ₃
309807	4-Me-1-Piz-CO	Pr	H	C ₂₃ H ₃₀ N ₆ O ₃

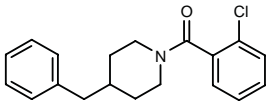
SOURCE – Bayer.

REFERENCES

1. Niewöhner, U. et al. (Bayer AG) *Novel imidazotriazinones and the use thereof.* DE 10010067, WO 0164677.

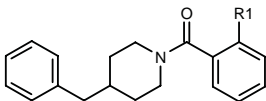
309900

1-(4-Benzylpiperidin-1-yl)-1-(2-chlorophenyl)methanone



C19 H20 Cl N O; Mol wt: 313.8260

ACTION – Selective p38 α kinase inhibitor (99% inhibition at 15 μ M), expected to be useful for the treatment of a variety of inflammatory and cardiac conditions including coronary artery disease, congestive heart failure, cardiomyopathy, restenosis, atherosclerosis, arthritis, multiple sclerosis, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, septic shock, stroke, etc. Other exemplified compounds are:



Compound	R1	Formula
309902	F	C ₁₉ H ₂₀ FNO
309903	Br	C ₁₉ H ₂₀ BrNO
309904	Me	C ₂₀ H ₂₃ NO
309905	CF3	C ₂₀ H ₂₀ F ₃ NO
309907	OMe	C ₂₀ H ₂₃ NO ₂

SOURCE – Scios.

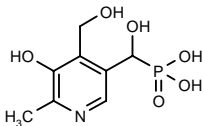
REFERENCES

1. Goehring, R.R. et al. (Scios Inc.) *Inhibitors of p38 α kinase.* WO 0164676.

MC-5723

306045

1-Hydroxy-1-[5-hydroxy-4-(hydroxymethyl)-6-methyl-pyridin-3-yl]methylphosphonic acid



C8 H12 N O6 P; Mol wt: 249.1578

ACTION – Pyridoxine phosphonate analogue potentially useful for the treatment of myocardial infarction.

SOURCE – Medigure.

REFERENCES

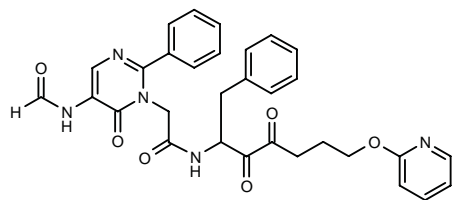
1. Haque, W. (Medigure Inc.) *Cardioprotective phosphonates and malonates.* WO 0164692.

2. *Medigure presents drug with potential for healing ischemic injury.* DailyDrugNews.com (Daily Essentials) 2001, July 13.

NK-3201*

267345

N-[1-Benzyl-2,3-dioxo-6-(2-pyridyloxy)hexyl]-2-[5-(formylamino)-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl]acetamide



C31 H29 N5 O6; Mol wt: 567.5991

ACTION – Orally active chymase inhibitor (IC_{50} = 2.5, 1.2 and 28 nM against human, dog and hamster enzyme, respectively) with no effect against angiotensin-converting enzyme (ACE) at up to 100 μ M. In dogs with intimal hyperplasia induced by carotid artery balloon injury, compound at a dose of 1 mg/kg/day p.o. (starting 5 days before balloon injury and continuing for 28 days) significantly reduced chymase activity and intimal areas compared with placebo-treated animals. The ratio of intimal to medial area was reduced by compound to about half that in the placebo-treated dogs. In dogs with carotid artery bypass graft, compound at a dose of 5 mg/kg/day p.o. for 28 days significantly suppressed the proliferation of grafted veins and attenuated the increase in chymase activity. Potentially useful for the prevention of intimal hyperplasia.

SOURCE – Nippon Kayaku.

REFERENCES

1. Suzuki, Y. and Ishida, K. (Nippon Kayaku Co., Ltd.) *Novel acetamide derivs. and protease inhibitors*. EP 0936216, US 6271238, WO 9809949.

2. Takai, S. et al. *Effects of a novel chymase inhibitor, NK3201, on canine intimal hyperplasia after balloon injury*. Circulation 2001, 104(17, Suppl. 2): Abst 1135.

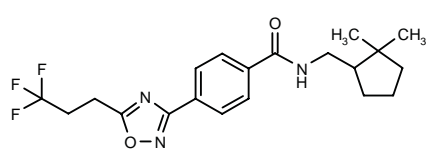
3. Takai, S. et al. *Oral administration of a specific chymase inhibitor, NK3201, inhibits vascular proliferation in grafted vein*. Life Sci 2001, 69(15): 1725.

*Identified compound **267345** (see **263799**) Drug Data Rep 1998, 020(09): 0762.

ANTIARRHYTHMIC DRUGS

310485

N-(2,2-Dimethylcyclopentylmethyl)-4-[5-(3,3,3-trifluoropropyl)-1,2,4-oxadiazol-3-yl]benzamide isomer A



C20 H24 F3 N3 O2; Mol wt: 395.4226

ACTION – Potent inhibitor of the slow component of the delayed rectifier potassium current (K_{vs} ; IC_{50} = 4 nM in isolated guinea pig ventricular myocytes) proven to only marginally block K_{vr} , K_{Na} and K_{Ca} at concentrations up to 10 μ M. Compound exhibited good oral bioavailability (23%) and a half-life after i.v. administration of 3.2 h in rats. Potentially useful for the prevention of arrhythmias.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Lloyd, J. et al. (Bristol-Myers Squibb Co.) *Benzoic acid derivs. and related cpds. as antiarrhythmic agents*. WO 9837068.

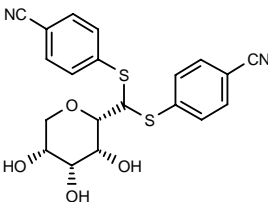
2. LLOYD, J. et al. *Design and synthesis of 4-substituted benzamides as potent, selective, and orally bioavailable IKS blockers*. J Med Chem 2001, 44(23): 3764.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

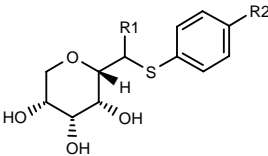
309094

2(S)-[1,1-Bis(4-cyanophenylsulfanyl)methyl]tetrahydropyran-3(R),4(R),5(R)-triol



C20 H18 N2 O4 S2; Mol wt: 414.5042

ACTION – Oral antithrombotic agent proven to inhibit thrombus formation (56% inhibition at 2 mg/kg p.o.) in a rat model of venous stasis thrombosis. Other related compounds are:



Compound	R1	R2	Isomer	Formula
309097	OMe	CN	(+)	C ₁₄ H ₁₇ NO ₅ S
309098	4-NO ₂ -PhS	NO ₂		C ₁₈ H ₁₈ N ₂ O ₈ S ₂
310261	OMe	CN	(-)	C ₁₄ H ₁₇ NO ₅ S

SOURCES – Gedeon Richter; Ivax Institute for Drug Research.

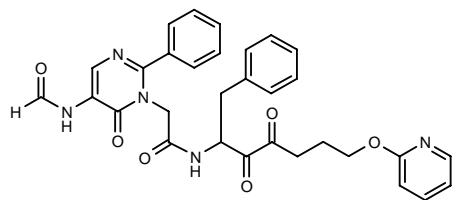
REFERENCES

1. Bozo, E. et al. *Orally active antithrombotic thioglycosides, Part XIII - Conversion of 2,6-anhydro- α -altrose and -mannose derivatives with 4-substituted phenyl thiols to prepare compounds with potential antithrombotic activity*. Carbohydr Res 2001, 332(3): 325.

NK-3201*

267345

N-[1-Benzyl-2,3-dioxo-6-(2-pyridyloxy)hexyl]-2-[5-(formylamino)-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl]acetamide



C31 H29 N5 O6; Mol wt: 567.5991

ACTION – Orally active chymase inhibitor (IC_{50} = 2.5, 1.2 and 28 nM against human, dog and hamster enzyme, respectively) with no effect against angiotensin-converting enzyme (ACE) at up to 100 μ M. In dogs with intimal hyperplasia induced by carotid artery balloon injury, compound at a dose of 1 mg/kg/day p.o. (starting 5 days before balloon injury and continuing for 28 days) significantly reduced chymase activity and intimal areas compared with placebo-treated animals. The ratio of intimal to medial area was reduced by compound to about half that in the placebo-treated dogs. In dogs with carotid artery bypass graft, compound at a dose of 5 mg/kg/day p.o. for 28 days significantly suppressed the proliferation of grafted veins and attenuated the increase in chymase activity. Potentially useful for the prevention of intimal hyperplasia.

SOURCE – Nippon Kayaku.

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1. Suzuki, Y. and Ishida, K. (Nippon Kayaku Co., Ltd.) *Novel acetamide derivs. and protease inhibitors*. EP 0936216, US 6271238, WO 9809949.

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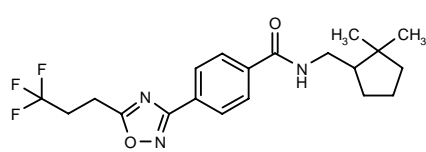
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*Identified compound **267345** (see **263799**) Drug Data Rep 1998, 020(09): 0762.

ANTIARRHYTHMIC DRUGS

310485

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ACTION – Potent inhibitor of the slow component of the delayed rectifier potassium current (K_{vs} ; IC_{50} = 4 nM in isolated guinea pig ventricular myocytes) proven to only marginally block K_{vr} , K_{Na} and K_{Ca} at concentrations up to 10 μ M. Compound exhibited good oral bioavailability (23%) and a half-life after i.v. administration of 3.2 h in rats. Potentially useful for the prevention of arrhythmias.

SOURCE – Bristol-Myers Squibb.

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1. Lloyd, J. et al. (Bristol-Myers Squibb Co.) *Benzoic acid derivs. and related cpds. as antiarrhythmic agents*. WO 9837068.

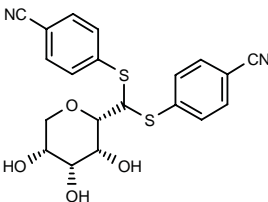
2. LLOYD, J. et al. *Design and synthesis of 4-substituted benzamides as potent, selective, and orally bioavailable IKS blockers*. J Med Chem 2001, 44(23): 3764.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

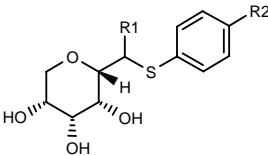
309094

2(S)-[1,1-Bis(4-cyanophenylsulfanyl)methyl]tetrahydropyran-3(R),4(R),5(R)-triol



C20 H18 N2 O4 S2; Mol wt: 414.5042

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Compound	R1	R2	Isomer	Formula
309097	OMe	CN	(+)	C ₁₄ H ₁₇ NO ₅ S
309098	4-NO ₂ -PhS	NO ₂		C ₁₈ H ₁₈ N ₂ O ₈ S ₂
310261	OMe	CN	(-)	C ₁₄ H ₁₇ NO ₅ S

SOURCES – Gedeon Richter; Ivax Institute for Drug Research.

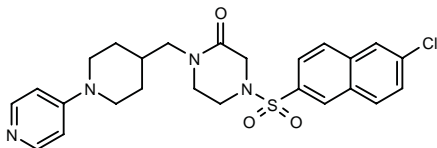
REFERENCES

1. Bozo, E. et al. *Orally active antithrombotic thioglycosides, Part XIII - Conversion of 2,6-anhydro- α -altrose and -mannose derivatives with 4-substituted phenyl thiols to prepare compounds with potential antithrombotic activity*. Carbohydr Res 2001, 332(3): 325.

M-55113

310009

4-(6-Chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)-piperidin-4-ylmethyl]piperazin-2-one



C25 H27 Cl N4 O3 S; Mol wt: 499.0323

ACTION – Anticoagulant, a potent factor Xa inhibitor (IC_{50} = 0.06 μ M) with > 3,000-fold selectivity over thrombin and trypsin (IC_{50} > 100 μ M). *In vitro* anticoagulant activity was demonstrated by the ability to double the clotting time in human plasma at 1.04 μ M.

SOURCE – Mochida.

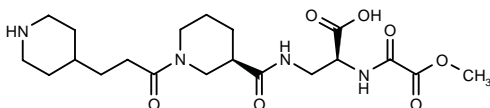
REFERENCES

1. Nishida, H. et al. (Mochida Pharmaceutical Co., Ltd.) *Aromatic cpds. having cyclic amino or salts thereof*. EP 1048652, WO 9933805.
2. Nishida, H. et al. *Synthesis and evaluation of 1-arylsulfonyl-3-piperazinone derivatives as factor Xa inhibitor*. Chem Pharm Bull 2001, 49(10): 1237.

ANTIPLATELET THERAPY

308985

2(S)-(Methoxalylamino)-3-[1-[3-(4-piperidiny)propionyl]-piperidin-3(R)-ylcarboxamido]propionic acid



C20 H32 N4 O7; Mol wt: 440.4938

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIb/IIIa) receptor antagonist proven to inhibit ADP-induced human platelet-rich plasma (PRP) aggregation with an IC_{50} of 0.085 μ M. A representative compound from a series of 2-acylamino- β -alanine derivatives.

SOURCE – Fujisawa.

REFERENCES

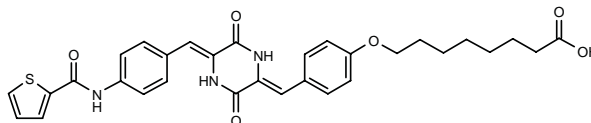
1. Ohkubo, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) *β -Alanine derivs. and their use as receptor antagonists*. WO 0160813.

THROMBOLYTICS

XR-11211

308876

(Z,Z)-8-[4-[3,6-Dioxo-5-[4-(thien-2-ylcarboxamido)-benzylidene]piperazin-2-ylidenemethyl]phenoxy]octanoic acid



C31 H31 N3 O6 S; Mol wt: 573.6669

ACTION – Potent inhibitor of plasminogen activator inhibitor-1 (PAI-1; IC_{50} = 0.20 μ M in a chromogenic assay) proven to inhibit fibrin formation (IC_{50} = 0.26 μ M in fibrin plate assay) and to prevent complex formation between tPA and PAI-1 (IC_{50} = 0.51 μ M). Potentially useful as a thrombolytic agent.

SOURCE – Xenova.

REFERENCES

1. Folkes, A. et al. *Design, synthesis and in vitro evaluation of potent, novel, small molecule inhibitors of plasminogen activator-1*. 11th RSC-SCI Med Chem Symp (Sept 9-12, Cambridge) 2001, Abst P3.
2. Folkes, A. et al. *Synthesis and in vitro evaluation of a series of diketopiperazine inhibitors of plasminogen activator inhibitor-1*. Bioorg Med Chem Lett 2001, 11(19): 2589.

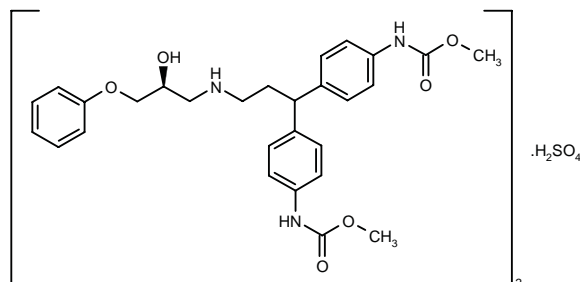
RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

309220

N-[4-[3-[2(S)-Hydroxy-3-phenoxypropylamino]-1-[4-(methoxycarbonylamino)phenyl]propyl]phenyl]carbamic acid methyl ester hemisulfate

N,N'-[3-[2(S)-Hydroxy-3-phenoxypropylamino]-propylidene]bis(1,4-phenylene)bis(carbamic acid methyl ester) hemisulfate

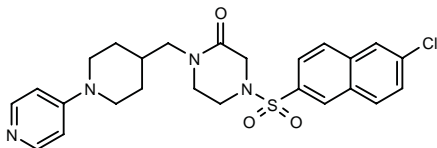


2 (C28 H33 N3 O6) . H2 O4 S; Mol wt: 1113.2450

M-55113

310009

4-(6-Chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)-piperidin-4-ylmethyl]piperazin-2-one



C25 H27 Cl N4 O3 S; Mol wt: 499.0323

ACTION – Anticoagulant, a potent factor Xa inhibitor (IC_{50} = 0.06 μ M) with > 3,000-fold selectivity over thrombin and trypsin (IC_{50} > 100 μ M). *In vitro* anticoagulant activity was demonstrated by the ability to double the clotting time in human plasma at 1.04 μ M.

SOURCE – Mochida.

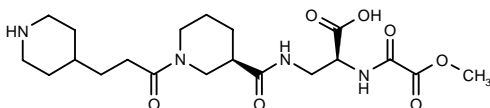
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2. Nishida, H. et al. *Synthesis and evaluation of 1-arylsulfonyl-3-piperazinone derivatives as factor Xa inhibitor*. Chem Pharm Bull 2001, 49(10): 1237.

ANTIPLATELET THERAPY

308985

2(S)-(Methoxalylamino)-3-[1-[3-(4-piperidiny)propionyl]-piperidin-3(R)-ylcarboxamido]propionic acid



C20 H32 N4 O7; Mol wt: 440.4938

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIb/IIIa) receptor antagonist proven to inhibit ADP-induced human platelet-rich plasma (PRP) aggregation with an IC_{50} of 0.085 μ M. A representative compound from a series of 2-acylamino- β -alanine derivatives.

SOURCE – Fujisawa.

REFERENCES

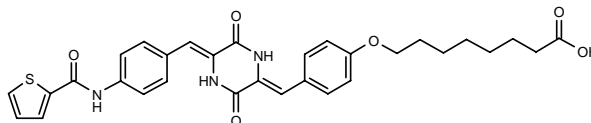
1. Ohkubo, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) *β -Alanine derivs. and their use as receptor antagonists*. WO 0160813.

THROMBOLYTICS

XR-11211

308876

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ACTION – Potent inhibitor of plasminogen activator inhibitor-1 (PAI-1; IC_{50} = 0.20 μ M in a chromogenic assay) proven to inhibit fibrin formation (IC_{50} = 0.26 μ M in fibrin plate assay) and to prevent complex formation between tPA and PAI-1 (IC_{50} = 0.51 μ M). Potentially useful as a thrombolytic agent.

SOURCE – Xenova.

REFERENCES

1. Folkes, A. et al. *Design, synthesis and in vitro evaluation of potent, novel, small molecule inhibitors of plasminogen activator-1*. 11th RSC-SCI Med Chem Symp (Sept 9-12, Cambridge) 2001, Abst P3.
2. Folkes, A. et al. *Synthesis and in vitro evaluation of a series of diketopiperazine inhibitors of plasminogen activator inhibitor-1*. Bioorg Med Chem Lett 2001, 11(19): 2589.

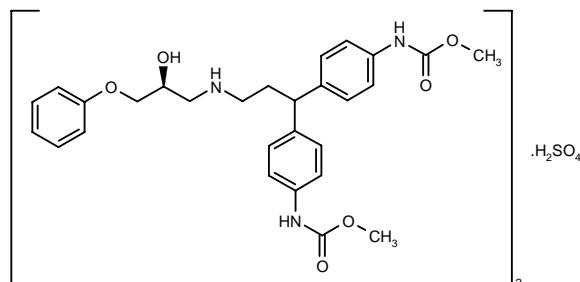
RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

309220

N-[4-[3-[2(S)-Hydroxy-3-phenoxypropylamino]-1-[4-(methoxycarbonylamino)phenyl]propyl]phenyl]carbamic acid methyl ester hemisulfate

N,N'-[3-[2(S)-Hydroxy-3-phenoxypropylamino]-propylidene]bis(1,4-phenylene)bis(carbamic acid methyl ester) hemisulfate



2 (C28 H33 N3 O6) . H2 O4 S; Mol wt: 1113.2450

ACTION – A representative compound from a series of aminoalcohol derivatives with β_3 -adrenoceptor-agonist activity. Compound was able to reduce the carbachol-induced increase in intravesicular pressure following i.v. administration to anesthetized dogs (1.8 μ g/kg). Potentially useful for the treatment of pollakiuria, urinary incontinence, obesity and diabetes.

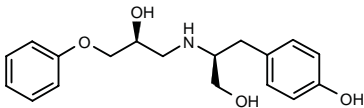
SOURCE – Fujisawa.

REFERENCES

1. Kayakiri, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Aminoalcohol derivs.* WO 0160786.

309442

4-[3-Hydroxy-2(S)-[2(S)-hydroxy-3-phenoxypropylamino]propyl]phenol



C18 H23 N O4; Mol wt: 317.3827

ACTION – A representative compound from a series of aminoalcohol derivatives active as selective β_3 -adrenoceptor agonists. Potentially useful for the treatment of urinary incontinence and pollakiuria, as demonstrated by a reduction in the carbachol-induced increase in intravesicular pressure following i.v. administration to anesthetized dogs at 0.032 mg/kg.

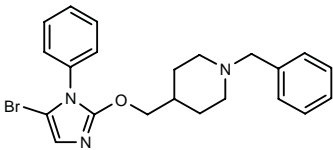
SOURCE – Fujisawa.

REFERENCES

1. Taniguchi, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Aminoalcohol derivs.* WO 0162705.

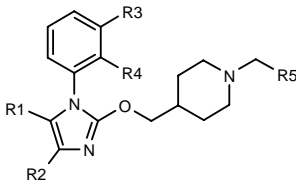
309787

1-Benzyl-4-(5-bromo-1-phenyl-1H-imidazol-2-yloxy)methyl)piperidine



C22 H24 Br N3 O; Mol wt: 426.3556

ACTION – Dual antagonist of muscarinic M_3 and 5-HT₄ receptors, potentially useful for the treatment of urge urinary incontinence, as well as irritable bowel syndrome, memory disturbances and obstructive airways diseases. Other specifically claimed haloimidazole derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
309788	Br	Me	H	H	Ph	C ₂₃ H ₂₆ BrN ₃ O
309789	Cl	Me	H	H	Ph	C ₂₃ H ₂₆ ClN ₃ O
309790	Cl	Me	H	H	3-OH-Ph	C ₂₃ H ₂₆ ClN ₃ O ₂
309791	Cl	Me	OH	H	3-OH-Ph	C ₂₃ H ₂₆ ClN ₃ O ₃
309792	Cl	Me	H	F	Ph	C ₂₃ H ₂₅ ClFN ₃ O
309793	Cl	Me	H	F	3-OH-Ph	C ₂₃ H ₂₅ ClFN ₃ O ₂
309794	H	Cl	H	H	Ph	C ₂₂ H ₂₄ ClN ₃ O
309795	Br	Br	H	H	Ph	C ₂₂ H ₂₅ Br ₂ N ₃ O
309796	Cl	Cl	H	H	Ph	C ₂₂ H ₂₃ Cl ₂ N ₃ O
309797	Cl	Me	H	F	CH ₂ CH=C(Me) ₂	C ₂₂ H ₂₉ ClFN ₃ O

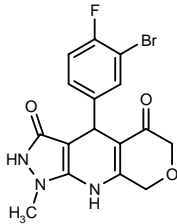
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Bovy, P.R. et al. (Sanofi-Synthélabo) *Haloimidazole derivs., their preparation and therapeutic use.* FR 2805816, WO 0164671.

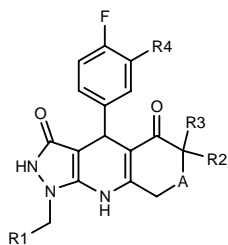
310087

4-(3-Bromo-4-fluorophenyl)-1-methyl-1,2,3,4,5,6,8,9-octahydropyrano[3,4-b]pyrazolo[4,3-e]pyridine-3,5-dione



C16 H13 Br F N3 O3; Mol wt: 394.1987

ACTION – Potassium channel opener shown to activate potassium channels in guinea pig urinary bladder cells with an EC₅₀ of 0.050 μ M. Potentially useful for the treatment of bladder hyperactivity, benign prostatic hyperplasia, dysmenorrhea, premature labor, urinary incontinence, erectile dysfunction, premature ejaculation, female sexual dysfunction, as well as other potassium channel-mediated disorders including asthma, epilepsy, Raynaud’s syndrome, intermittent claudication, migraine, pain, pollakiuria, enuresis, alopecia, ischemia, eating disorders, functional bowel disorders and neurodegeneration. Other exemplified nitrogen-containing tricyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
310089	H	Me	Me	I	-CH2-	C ₁₉ H ₁₉ FIN ₃ O ₂
310090	Me	H	H	Br	bond	C ₁₇ H ₁₅ BrFN ₃ O ₂
310091	H	H	H	I	bond	C ₁₆ H ₁₃ FIN ₃ O ₂
310092	H	Me	Me	Br	-CH2-	C ₁₉ H ₁₉ BrFN ₃ O ₂

SOURCE – Abbott.

REFERENCES

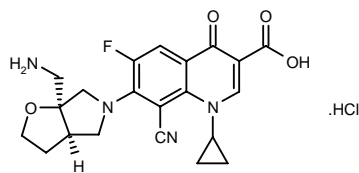
1. Drizin, I. et al. (Abbott Laboratories Inc.) *Tricyclic dihydropyrazolone and tricyclic dihydroisoxazolone potassium channel openers*. WO 0166544.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

309607

(+)-7-[(3a*R*,6a*S*)-6a-(Aminomethyl)perhydrofuro[2,3-*c*]pyrrol-5-yl]-8-cyano-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride



C21 H21 F N4 O4 . HCl; Mol wt: 448.8798

ACTION – A representative compound from a series of quinolones and naphthyridones for use in the treatment of *Helicobacter pylori* infection and gastroduodenal disorders associated therewith. Compound displayed an MIC value of 0.03 mg/l against *H. pylori* strains 008 and 11637. *In vivo*, it was more effective than ciprofloxacin when administered to *H. pylori*-infected mice twice daily at 10 mg/kg for 3 days.

SOURCE – Bayer.

REFERENCES

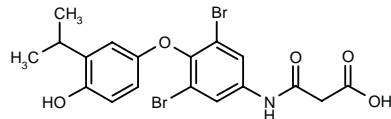
1. Petersen, U. et al. (Bayer AG) *Use of 7-(1-aminomethyl-2-oxa-7-azabicyclo-[3.3.0]oct-7-yl)-quinolone carboxylic acid and naphthyridone carboxylic acid derivs. for treating Helicobacter pylori infections and the gastroduodenal diseases associated therewith*. DE 19652219, US 6288081, WO 9826768.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

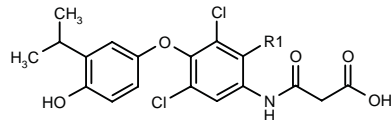
308908

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)-phenyl]malonamic acid



C18 H17 Br2 N O5; Mol wt: 487.1423

ACTION – Selective thyroid hormone receptor-β agonist with potential for the treatment or prevention of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure and skin disorders. Other specifically claimed compounds from this series of aniline derivatives include the following:



Compound	R1	Formula
308909	H	C ₁₈ H ₁₇ Cl ₂ NO ₅
308911	Me	C ₁₉ H ₁₉ Cl ₂ NO ₅

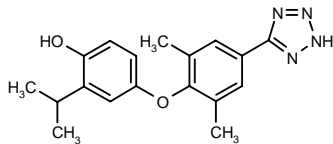
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Friends, T.J. et al. (Bristol-Myers Squibb Co.) *Aniline-derived ligands for the thyroid receptor*. WO 0160784.

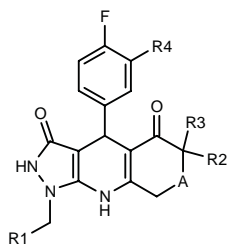
309267

4-[2,6-Dimethyl-4-(2*H*-tetrazol-5-yl)phenoxy]-2-iso-propylphenol



C18 H20 N4 O2; Mol wt: 324.3820

ACTION – Agent with the ability to bind to thyroid hormone receptors, potentially useful for the treatment of diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, hyperthyroidism, depression, obesity, osteoporosis, thyroid cancer, glaucoma, cardiac arrhythmias and congestive heart failure. Other specifically claimed tetrazole compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
310089	H	Me	Me	I	-CH2-	C ₁₉ H ₁₉ FIN ₃ O ₂
310090	Me	H	H	Br	bond	C ₁₇ H ₁₅ BrFN ₃ O ₂
310091	H	H	H	I	bond	C ₁₆ H ₁₃ FIN ₃ O ₂
310092	H	Me	Me	Br	-CH2-	C ₁₉ H ₁₉ BrFN ₃ O ₂

SOURCE – Abbott.

REFERENCES

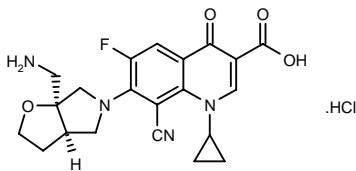
1. Drizin, I. et al. (Abbott Laboratories Inc.) *Tricyclic dihydropyrazolone and tricyclic dihydroisoxazolone potassium channel openers*. WO 0166544.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

309607

(+)-7-[(3a*R*,6a*S*)-6a-(Aminomethyl)perhydrofuro[2,3-*c*]pyrrol-5-yl]-8-cyano-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride



C21 H21 F N4 O4 . HCl; Mol wt: 448.8798

ACTION – A representative compound from a series of quinolones and naphthyridones for use in the treatment of *Helicobacter pylori* infection and gastroduodenal disorders associated therewith. Compound displayed an MIC value of 0.03 mg/l against *H. pylori* strains 008 and 11637. *In vivo*, it was more effective than ciprofloxacin when administered to *H. pylori*-infected mice twice daily at 10 mg/kg for 3 days.

SOURCE – Bayer.

REFERENCES

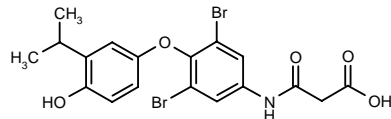
1. Petersen, U. et al. (Bayer AG) *Use of 7-(1-aminomethyl-2-oxa-7-azabicyclo-[3.3.0]oct-7-yl)-quinolone carboxylic acid and naphthyridone carboxylic acid derivs. for treating Helicobacter pylori infections and the gastroduodenal diseases associated therewith*. DE 19652219, US 6288081, WO 9826768.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

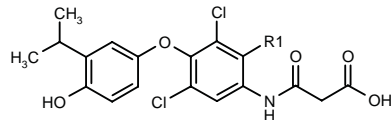
308908

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)-phenyl]malonamic acid



C18 H17 Br2 N O5; Mol wt: 487.1423

ACTION – Selective thyroid hormone receptor-β agonist with potential for the treatment or prevention of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure and skin disorders. Other specifically claimed compounds from this series of aniline derivatives include the following:



Compound	R1	Formula
308909	H	C ₁₈ H ₁₇ Cl ₂ NO ₅
308911	Me	C ₁₉ H ₁₉ Cl ₂ NO ₅

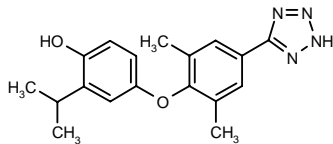
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Friends, T.J. et al. (Bristol-Myers Squibb Co.) *Aniline-derived ligands for the thyroid receptor*. WO 0160784.

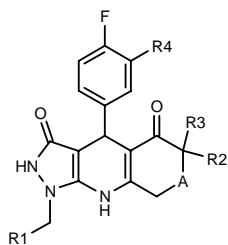
309267

4-[2,6-Dimethyl-4-(2*H*-tetrazol-5-yl)phenoxy]-2-isopropylphenol



C18 H20 N4 O2; Mol wt: 324.3820

ACTION – Agent with the ability to bind to thyroid hormone receptors, potentially useful for the treatment of diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, hyperthyroidism, depression, obesity, osteoporosis, thyroid cancer, glaucoma, cardiac arrhythmias and congestive heart failure. Other specifically claimed tetrazole compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
310089	H	Me	Me	I	-CH2-	C ₁₉ H ₁₉ FIN ₃ O ₂
310090	Me	H	H	Br	bond	C ₁₇ H ₁₅ BrFN ₃ O ₂
310091	H	H	H	I	bond	C ₁₆ H ₁₃ FIN ₃ O ₂
310092	H	Me	Me	Br	-CH2-	C ₁₉ H ₁₉ BrFN ₃ O ₂

SOURCE – Abbott.

REFERENCES

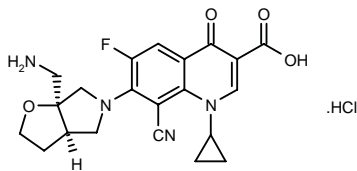
1. Drizin, I. et al. (Abbott Laboratories Inc.) *Tricyclic dihydropyrazolone and tricyclic dihydroisoxazolone potassium channel openers*. WO 0166544.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

309607

(+)-7-[(3a*R*,6a*S*)-6a-(Aminomethyl)perhydrofuro[2,3-*c*]pyrrol-5-yl]-8-cyano-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride



C21 H21 F N4 O4 . HCl; Mol wt: 448.8798

ACTION – A representative compound from a series of quinolones and naphthyridones for use in the treatment of *Helicobacter pylori* infection and gastroduodenal disorders associated therewith. Compound displayed an MIC value of 0.03 mg/l against *H. pylori* strains 008 and 11637. *In vivo*, it was more effective than ciprofloxacin when administered to *H. pylori*-infected mice twice daily at 10 mg/kg for 3 days.

SOURCE – Bayer.

REFERENCES

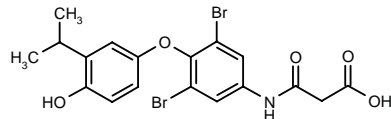
1. Petersen, U. et al. (Bayer AG) *Use of 7-(1-aminomethyl-2-oxa-7-azabicyclo-[3.3.0]oct-7-yl)-quinolone carboxylic acid and naphthyridone carboxylic acid derivs. for treating Helicobacter pylori infections and the gastroduodenal diseases associated therewith*. DE 19652219, US 6288081, WO 9826768.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

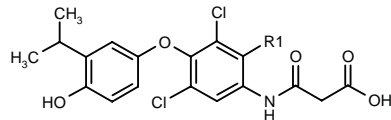
308908

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)-phenyl]malonamic acid



C18 H17 Br2 N O5; Mol wt: 487.1423

ACTION – Selective thyroid hormone receptor-β agonist with potential for the treatment or prevention of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure and skin disorders. Other specifically claimed compounds from this series of aniline derivatives include the following:



Compound	R1	Formula
308909	H	C ₁₈ H ₁₇ Cl ₂ NO ₅
308911	Me	C ₁₉ H ₁₉ Cl ₂ NO ₅

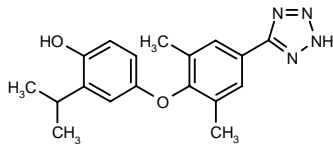
SOURCE – Bristol-Myers Squibb.

REFERENCES

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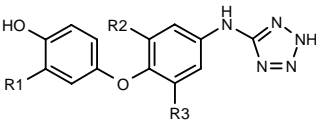
309267

4-[2,6-Dimethyl-4-(2*H*-tetrazol-5-yl)phenoxy]-2-isopropylphenol



C18 H20 N4 O2; Mol wt: 324.3820

ACTION– Agent with the ability to bind to thyroid hormone receptors, potentially useful for the treatment of diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, hyperthyroidism, depression, obesity, osteoporosis, thyroid cancer, glaucoma, cardiac arrhythmias and congestive heart failure. Other specifically claimed tetrazole compounds include the following:



Compound	R1	R2=R3	Formula
309270	cyclobutyl-CH2SO2	Me	C ₂₀ H ₂₃ N ₅ O ₄ S
309271	cyclohexyl-CH2SO2	Me	C ₂₂ H ₂₇ N ₅ O ₄ S
309272	CONHMe	Cl	C ₁₅ H ₁₂ Cl ₂ N ₆ O ₃
309273	cyclopentyl-NHCO	Cl	C ₁₉ H ₁₈ Cl ₂ N ₆ O ₃
309275	(R)-cyclohexyl-CH(Me)NHCO	Cl	C ₂₂ H ₂₄ Cl ₂ N ₆ O ₃
309276	CON(Me)CH(i-Pr) ₂	Cl	C ₂₂ H ₂₆ Cl ₂ N ₆ O ₃

SOURCE – Pfizer.

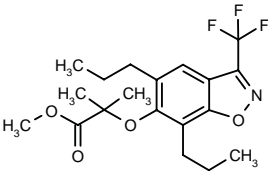
REFERENCES

1. Chiang, Y.-C.P. and Aspnes, G.E. (Pfizer Products Inc.) *Tetrazole cpds. as thyroid receptor ligands*. EP 1127882, JP 2001226359.

ANTIDIABETIC DRUGS

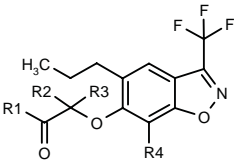
308993

2-[5,7-Dipropyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yloxy]-2-methylpropionic acid methyl ester



C₁₉ H₂₄ F₃ N O₄; Mol wt: 387.3956

ACTION – Peroxisome proliferator-activated receptor PPAR α and/or PPAR γ agonist, with potential for the treatment, control and prevention of non-insulin-dependent diabetes mellitus (NIDDM), hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, obesity, vascular restenosis and inflammation, among others. Other specifically claimed compounds from this series of aryloxyacetic acid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
308994	OH	Me	Me	Pr	C ₁₈ H ₂₂ F ₃ NO ₄
308995	OH	Me	Me	Cl	C ₁₅ H ₁₅ ClF ₃ NO ₄
308996	OEt	Et	H	Pr	C ₂₀ H ₂₆ F ₃ NO ₄
308997	OH	Et	Pr	Pr	C ₂₁ H ₂₈ F ₃ NO ₄
308998	OCH2CH2NHAc	Me	Me	Pr	C ₂₂ H ₂₉ F ₃ N ₂ O ₅
308999	NH2	Me	Me	Pr	C ₁₈ H ₂₃ F ₃ N ₂ O ₃
309000	OH	-(CH2)4-		Pr	C ₂₀ H ₂₄ F ₃ NO ₄

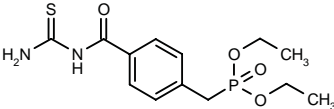
SOURCE – Merck & Co.

REFERENCES

1. Liu, K. et al. (Merck & Co., Inc.) *Aryloxyacetic acids for diabetes and lipid disorders*. WO 0160807.

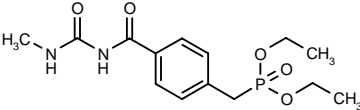
309314

4-(Thioureidocarbonyl)benzylphosphonic acid diethyl ester



C₁₃ H₁₉ N₂ O₄ P S; Mol wt: 330.3431

ACTION – Agent with glucose- and lipid-lowering properties, potentially useful for the treatment of hyperlipidemia and diabetes. It induced a 53% decrease of blood glucose levels in dexamethasone-treated rats when orally administered at 100 mg/kg for 4 days. Another exemplified phosphonic acid diester is:



309318: C₁₄ H₂₁ N₂ O₅ P

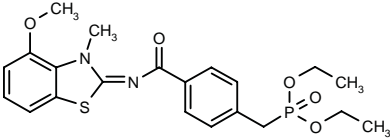
SOURCE – Otsuka.

REFERENCES

1. Miyata, K. et al. (Otsuka Pharmaceutical Co., Ltd.) *Phosphonic acid diester derivs*. JP 2001206890.

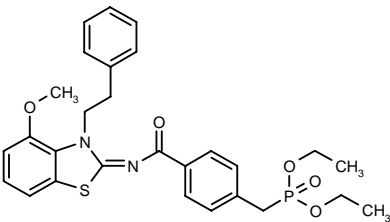
309320

4-[N-(4-Methoxy-3-methyl-2,3-dihydrobenzothiazol-2-ylidene)carbamoyl]benzylphosphonic acid diethyl ester



C₂₁ H₂₅ N₂ O₅ P S; Mol wt: 448.4775

ACTION – Agent with glucose- and lipid-lowering properties, potentially useful for the treatment of hyperlipidemia and diabetes. Another exemplified phosphonic acid diester is:



309322: C₂₈ H₃₁ N₂ O₅ P S

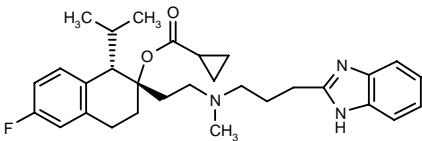
SOURCE – Otsuka.

REFERENCES

1. Miyata, K. et al. (Otsuka Pharmaceutical Co., Ltd.) *Phosphonic acid diester derivs.* JP 2001206891.

309373

Cyclopropanecarboxylic acid 2(S)-[2-[N-[3-(1H-benzimidazol-2-yl)propyl]-N-methylamino]ethyl]-6-fluoro-1(S)-isopropyl-1,2,3,4-tetrahydronaphthalen-2-yl ester



C30 H38 F N3 O2; Mol wt: 491.6472

ACTION – Agent for the treatment and prevention of type 1 and type 2 diabetes, as well as microvascular and macrovascular diseases associated with diabetes such as retinopathy, nephropathy, neuropathy, gangrene, myocardial infarction, cerebral stroke and atherosclerosis, a specifically claimed compound from a series of mibefradil analogues that act by blocking T-type calcium channels and reported to be devoid of any effect on L-type calcium channels.

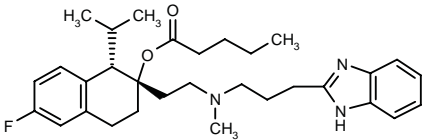
SOURCES – Novo Nordisk; South Alabama Medical Science Foundation, Mobile, AL (US).

REFERENCES

1. Li, M. et al. (South Alabama Medical Science Foundation; Novo Nordisk A/S) *Tetrahydronaphthalene derivs. and their use.* WO 0162741.

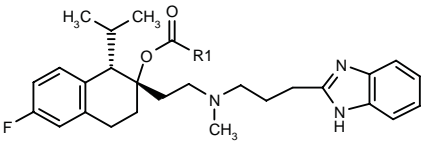
309374

Pentanoic acid 2(S)-[2-[N-[3-(1H-benzimidazol-2-yl)propyl]-N-methylamino]ethyl]-6-fluoro-1(S)-isopropyl-1,2,3,4-tetrahydronaphthalen-2-yl ester



C31 H42 F N3 O2; Mol wt: 507.6898

ACTION – Agent for the treatment and prevention of type 1 and type 2 diabetes, as well as microvascular and macrovascular diseases associated with diabetes such as retinopathy, nephropathy, neuropathy, gangrene, myocardial infarction, cerebral stroke and atherosclerosis, a T-type calcium channel blocker reported to be devoid of any effect on L-type calcium channels. Other specifically claimed compounds from this series of mibefradil analogues are:



Compound	R1	Formula
309375	i-Pr	C ₃₀ H ₄₀ FN ₃ O ₂
309376	i-Bu	C ₃₁ H ₄₂ FN ₃ O ₂
309377	CH(Me)Et	C ₃₁ H ₄₂ FN ₃ O ₂
309378	cyclopropyl-CH2	C ₃₁ H ₄₀ FN ₃ O ₂
309379	cyclopentyl-CH2	C ₃₃ H ₄₄ FN ₃ O ₂

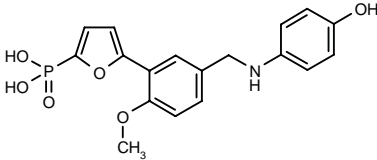
SOURCES – Novo Nordisk; South Alabama Medical Science Foundation, Mobile, AL (US).

REFERENCES

1. Li, M. et al. (South Alabama Medical Science Foundation; Novo Nordisk A/S) *Mibefradil analogues and their use.* WO 0162740.

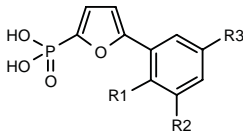
310078

5-[5-(4-Hydroxyphenylaminomethyl)-2-methoxyphenyl]-furan-2-ylphosphonic acid



C18 H18 N O6 P; Mol wt: 375.3152

ACTION – An inhibitor of fructose-1,6-bisphosphatase (FBPase; IC₅₀ = 0.14 μM against human liver enzyme), with potential in the treatment of diabetes and other diseases where the inhibition of gluconeogenesis, control of blood glucose levels, reduction in glycogen storage or reduction in insulin levels is beneficial. Other exemplified compounds from this series of aryl derivatives containing a phosphonate or phosphoramidate group include the following:



Compound	R1	R2	R3	Formula
310079	H	NO2	NO2	C ₁₀ H ₇ N ₂ O ₈ P
310080	OMe	H	Cl	C ₁₁ H ₁₀ ClO ₅ P
310081	OMe	H	4-NH2-PhNHCH2	C ₁₈ H ₁₉ N ₂ O ₅ P

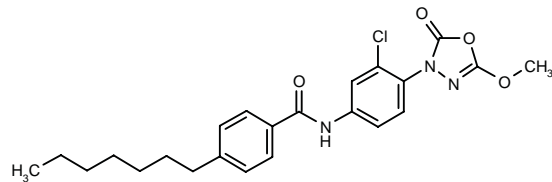
SOURCE – Metabasis Therapeutics.

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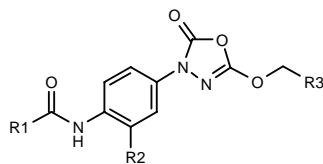
310093

N-[3-Chloro-4-(5-methoxy-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)phenyl]-4-heptylbenzamide



C23 H26 Cl N3 O4; Mol wt: 443.9284

ACTION – Antidiabetic agent with the ability to inhibit hormone-sensitive lipase (HSL; IC₅₀ = 0.02 μM), expected to be useful for the treatment of non-insulin-dependent diabetes mellitus and related disorders. Other exemplified 1,3,4-oxadiazol-2-one derivatives include the following:



Compound	R1	R2	R3	Formula
310094	OCH2Ph	Me	H	C ₁₈ H ₁₇ N ₃ O ₅
310095	4-t-Bu-Ph	H	H	C ₂₀ H ₂₁ N ₃ O ₄
310096	OCH2Ph	Me	Me	C ₁₉ H ₁₉ N ₃ O ₅
310097	2-F-Ph	H	H	C ₁₆ H ₁₂ FN ₃ O ₄
310098	C10H21	H	H	C ₂₀ H ₂₉ N ₃ O ₄
310099	(CH2)3COPh	H	H	C ₂₀ H ₁₉ N ₃ O ₅

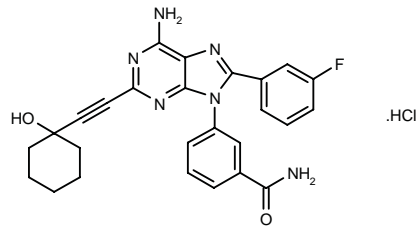
SOURCE – Aventis Pharma.

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310424

3-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)ethynyl]-9H-purin-9-yl]benzamide hydrochloride



C26 H23 F N6 O2 . HCl; Mol wt: 506.9666

ACTION – An inhibitor of hepatic glucose production (IC₅₀ = 0.017 μM) with adenosine A_{2B} receptor-agonist activity (IC₅₀ = 2.5 nM in CHO.K1 cells expressing human A_{2B} receptors) and 72- and 5.2-fold selectivity over human A₁ and A_{2A} receptors, respectively. Potentially useful as an antidiabetic agent.

SOURCE – Eisai.

REFERENCES

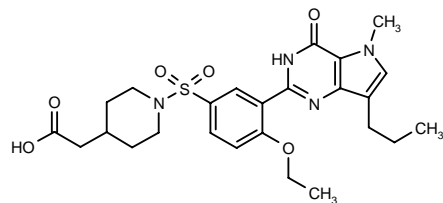
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TREATMENT OF MALE SEXUAL DYSFUNCTION

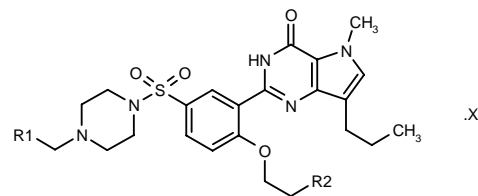
309152

2-[1-[4-Ethoxy-3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenylsulfonyl]piperidin-4-yl]acetic acid

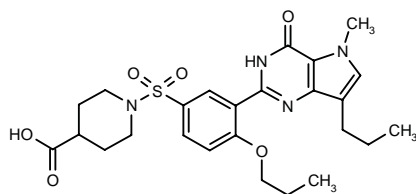


C25 H32 N4 O6 S; Mol wt: 516.6158

ACTION – A selective phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 0.27 nM), potentially useful for the treatment of impotence, female sexual dysfunction, angina, hypertension, congestive heart failure, renal failure, atherosclerosis, peripheral vascular disease, Raynaud’s disease, stroke, bronchitis, asthma, allergic rhinitis, glaucoma and irritable bowel disease. Other exemplified pyrrolopyrimidinone derivatives are:



Compound	R1	R2	X	Formula
309153	H	H		C ₂₃ H ₃₁ N ₅ O ₄ S
309154	H	Me		C ₂₄ H ₃₃ N ₅ O ₄ S
309156	CH2CH2F	H		C ₂₅ H ₃₄ FN ₅ O ₄ S
309158	CH2CH2F	H	.H2SO4	C ₂₅ H ₃₄ FN ₅ O ₄ S.H ₂ O ₄ S
309159	CH2Cl	H		C ₂₄ H ₃₂ ClN ₅ O ₄ S
309160	CH2CH2Cl	H	HCl	C ₂₅ H ₃₄ ClN ₅ O ₄ S.HCl
309162	5-tetrazolyl	H		C ₂₄ H ₃₁ N ₆ O ₄ S
309163	5-tetrazolyl	Me		C ₂₅ H ₃₃ N ₆ O ₄ S



309161: C25 H32 N4 O6 S

SOURCES – In2Gen; SK Chemicals.

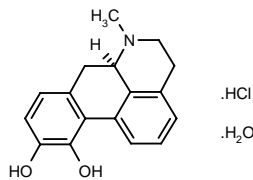
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APOMORPHINE HYDROCHLORIDE
BANM; USAN **New use/new formulation**

231571

(*R*)-6-Methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]-quinoline-10,11-diol hydrochloride hemihydrate



C17 H17 N O2 . HCl . H2O; Mol wt: 321.8020

ACTION – Dopamine D2 agonist.

INDICATION – Treatment of erectile dysfunction.

PRESENTATION – Sublingual tablets containing 2 and 3 mg apomorphine hydrochloride equivalent to 1.71 mg and 2.56 mg apomorphine, respectively.

PROPRIETARY NAMES AND SOURCES – *Ixense* (Takeda; DE, FR); *Uprima* (Abbott; ES, GB); developed by TAP Pharmaceutical (Abbott–Takeda joint venture) under license from Pentech.

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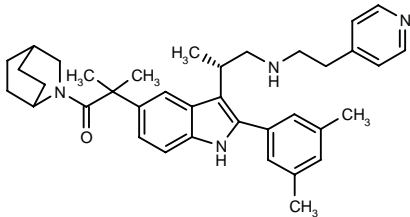
42. *Uprima to be considered for ED next week by FDA advisory committee*. DailyDrugNews.com (Daily Essentials) 2000, April 5.

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TREATMENT OF GYNECOLOGICAL DISORDERS

308881

2(S)-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]-*N*-[2-(4-pyridyl)ethyl]propan-1-amine



C37 H46 N4 O; Mol wt: 562.7974

ACTION – Potent gonadotropin-releasing hormone (GnRH, also known as luteinizing hormone-releasing hormone, LHRH) antagonist with an IC₅₀ value of 0.6 nM for the human GnRH receptor and an IC₅₀ of 7.2 nM for inhibition of phosphatidylinositol (PI) hydrolysis in CHO cells transfected with the human GnRH receptor. Compound exhibited promising pharmacokinetic properties in rats, dogs and monkeys, with respective oral bioavailabilities of 8, 25 and 21% and a terminal half-life of 1 h in rats, 3.9 h in dogs and 3.3 h in monkeys. In a castrated rat model, compound dose-dependently inhibited LH release, giving complete suppression of circulating LH levels for 13 h at the dose of 10 mg/kg p.o. Potentially useful for the treatment of hormone-dependent cancers, uterine fibroids, endometriosis and for short-term application in assisted reproduction protocols.

SOURCE – Merck & Co.

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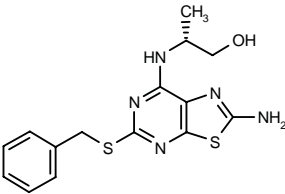
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DERMATOLOGIC DRUGS

ANTIPSORIATICS

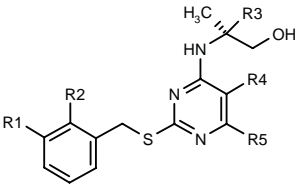
308781

2(R)-[2-Amino-5-(benzylsulfanyl)thiazolo[5,4-*d*]pyrimidin-7-ylamino]propan-1-ol

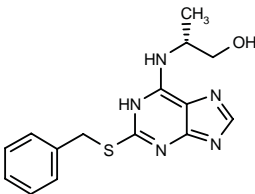


C15 H17 N5 O S2; Mol wt: 347.4653

ACTION – Agent for the treatment or prevention of chemokine-mediated disorders, particularly psoriasis and chronic obstructive pulmonary disease (COPD), a chemokine CXCR2 receptor antagonist. Other specifically claimed compounds from this series of fused pyrimidine derivatives are:



Compound	R1=R2	R3	R4,R5	Formula
308782	H	H	-NHCO-	C ₁₅ H ₁₆ N ₄ O ₂ S ₂
308785	F	H	-CH=NNH-	C ₁₅ H ₁₅ F ₂ N ₆ OS
308786	H	Me	-N=NNH-	C ₁₅ H ₁₈ N ₆ OS



308784: C15 H17 N5 O S

SOURCE – AstraZeneca.

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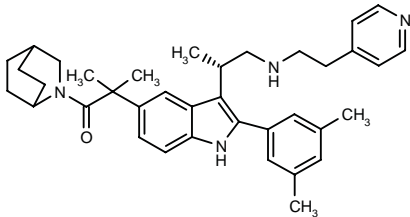
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TREATMENT OF GYNECOLOGICAL DISORDERS

308881

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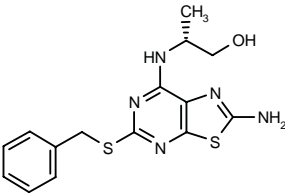
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DERMATOLOGIC DRUGS

ANTIPSORIATICS

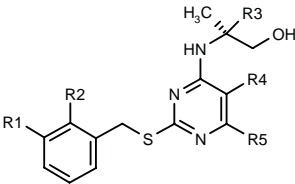
308781

2(R)-[2-Amino-5-(benzylsulfanyl)thiazolo[5,4-*d*]pyrimidin-7-ylamino]propan-1-ol

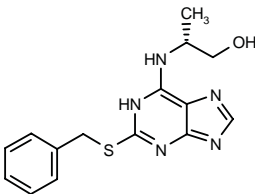


C15 H17 N5 O S2; Mol wt: 347.4653

ACTION – Agent for the treatment or prevention of chemokine-mediated disorders, particularly psoriasis and chronic obstructive pulmonary disease (COPD), a chemokine CXCR2 receptor antagonist. Other specifically claimed compounds from this series of fused pyrimidine derivatives are:



Compound	R1=R2	R3	R4,R5	Formula
308782	H	H	-NHCO-	C ₁₅ H ₁₆ N ₄ O ₂ S ₂
308785	F	H	-CH=NNH-	C ₁₅ H ₁₅ F ₂ N ₆ OS
308786	H	Me	-N=NNH-	C ₁₅ H ₁₈ N ₆ OS



308784: C15 H17 N5 O S

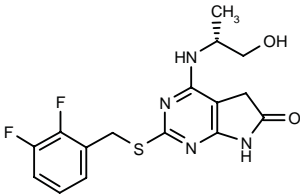
SOURCE – AstraZeneca.

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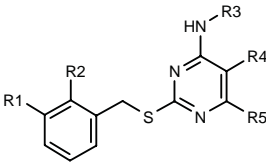
308787

2-(2,3-Difluorobenzylsulfanyl)-4-[2-hydroxy-1 (*R*)-methyl-ethylamino]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



C16 H16 F2 N4 O2 S; Mol wt: 366.3904

ACTION – Agent for the treatment or prevention of chemokine-mediated disorders, particularly psoriasis and chronic obstructive pulmonary disease (COPD), a chemokine CXCR2 receptor antagonist. Other specifically claimed compounds from this series of fused pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4,R5	Formula
308788	F	F	H	-CH2CONH-	C ₁₃ H ₁₀ F ₂ N ₄ OS
308789	F	F	(<i>R</i>)-CH(Et)CH2OH	-N=C(NH2)NH-	C ₁₆ H ₁₈ F ₂ N ₆ OS
308790	Me	H	(<i>R</i>)-CH(Me)CH2OH	-N=C(NH2)NH-	C ₁₆ H ₂₀ N ₆ OS
308791	H	Br	(<i>R</i>)-CH(Me)CH2OH	-N=C(NH2)NH-	C ₁₅ H ₁₇ BrN ₆ OS
308792	Cl	F	(<i>R</i>)-CH(Me)CH2OH	-N=C(NH2)NH-	C ₁₅ H ₁₆ ClFN ₆ OS
308793	-OCH2O-	(<i>R</i>)-CH(Me)CH2OH	-N=C(NH2)NH-		C ₁₆ H ₁₈ N ₆ O ₃ S

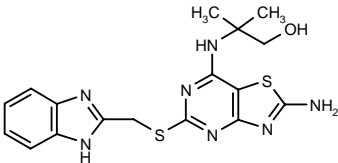
SOURCE – AstraZeneca.

REFERENCES

1. Bonnert, R. et al. (AstraZeneca AB) *Pyrimidine cpds. and their use as modulators of chemokine receptor activity*. WO 0158902.

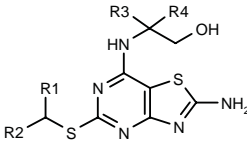
308794

2-[2-Amino-5-(1 *H*-benzimidazol-2-ylmethylsulfanyl)-thiazolo[4,5-*d*]pyrimidin-7-ylamino]-2-methylpropan-1-ol



C17 H19 N7 O S2; Mol wt: 401.5171

ACTION – Agent for the treatment or prevention of chemokine-mediated disorders, particularly psoriasis and chronic obstructive pulmonary disease (COPD), a chemokine CXCR2 receptor antagonist. Other specifically claimed compounds from this series of thiazolopyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
308795	2-thienyl	Me	Me	Me	C ₁₅ H ₁₉ N ₅ OS ₃
308796	3,5-(Me)2-4-isoxazolyl	H	H	(<i>R</i>)-Me	C ₁₄ H ₁₈ N ₆ O ₂ S ₂
308797	2-(AcNH)-4-thiazolyl	H	H	(<i>R</i>)-Me	C ₁₄ H ₁₇ N ₇ O ₂ S ₃
308798	2-Me-4-thiazolyl	H	H	CH2OH	C ₁₃ H ₁₆ N ₆ O ₂ S ₃
308799	2-Me-4-thiazolyl	H	Me	Me	C ₁₄ H ₁₈ N ₆ OS ₃

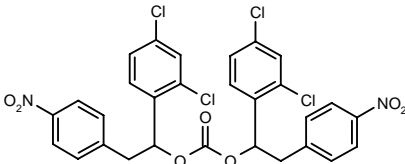
SOURCE – AstraZeneca.

REFERENCES

1. Bonnert, R. et al. (AstraZeneca AB) *Thiazolopyrimidines and their use as modulators of chemokine receptor activity*. WO 0158907.

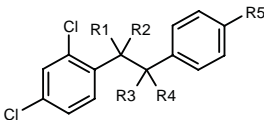
309001

Carbonic acid bis[1-(2,4-dichlorophenyl)-2-(4-nitrophenyl)ethyl] diester

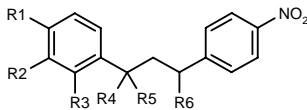


C29 H20 Cl4 N2 O7; Mol wt: 650.2960

ACTION – Agent with the ability to reduce the metabolism of retinoic acid (RA) through inhibition of RA-inducible P-450 RA-metabolizing enzymes (91.27% inhibition at 100 μM in rat liver microsomes). Potentially useful for the treatment of skin disorders such as psoriasis, acne or actinic keratosis, and cancer. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
309002	-O-		-O-		NO2	C ₁₄ H ₇ Cl ₂ NO ₄
309003	H	H	H	OH	NO2	C ₁₄ H ₁₁ Cl ₂ NO ₃
309004	H	H	-OCH2CH2O-		NO2	C ₁₆ H ₁₃ Cl ₂ NO ₄
309005	-O-		Br	Br	NO2	C ₁₄ H ₇ Br ₂ Cl ₂ NO ₃
309006	-OCH2CH2O-		H	H	NO2	C ₁₆ H ₁₃ Cl ₂ NO ₄
309010	H	OH	-O-		N(Me)2	C ₁₆ H ₁₅ Cl ₂ NO ₂



Compound	R1	R2	R3	R4	R5	R6	Formula
309007	H	Cl	H	-O-		CO2Me	C ₁₇ H ₁₄ ClNO ₅
309008	Cl	H	Cl	H	-OCO-		C ₁₆ H ₁₁ Cl ₂ NO ₄
309009	Cl	H	Cl	H	OH	CH2OH	C ₁₆ H ₁₅ Cl ₂ NO ₄

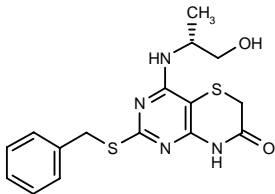
SOURCE – University College Cardiff, Cardiff (GB).

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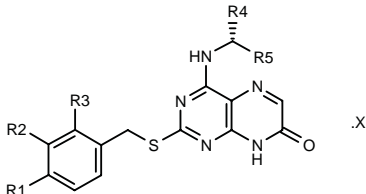
309529

2-(Benzylsulfanyl)-4-[2-hydroxy-1 (*R*)-methylethylamino]-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]thiazin-7-one



C16 H18 N4 O2 S2; Mol wt: 362.4762

ACTION – Chemokine CXCR2 receptor antagonist, potentially useful for the treatment of psoriasis and chronic obstructive pulmonary disease (COPD). Other specifically claimed pteridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
309530	H	F	F	Me	CH2OH		C ₁₆ H ₁₅ F ₂ N ₅ O ₂ S
309531	OMe	Cl	H	H	CH2NH2	CF3CO2H	C ₁₆ H ₁₇ ClN ₅ O ₂ S .C ₂ HF ₃ O ₂
309532	H	Cl	H	Me	CH2OH		C ₁₆ H ₁₆ ClN ₅ O ₂ S
309533	H	CF3	F	Me	CH2OH		C ₁₇ H ₁₅ F ₄ N ₅ O ₂ S
309534	H	F	F	Me	Me		C ₁₆ H ₁₅ F ₂ N ₅ OS
309535	H	F	F	H	CH(OH)-CH2NH2		C ₁₆ H ₁₆ F ₂ N ₅ O ₂ S
309536	H	F	F	CO2Et	CH2OH		C ₁₈ H ₁₇ F ₂ N ₅ O ₄ S

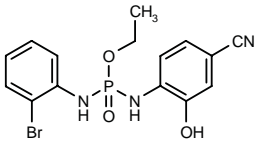
SOURCE – AstraZeneca.

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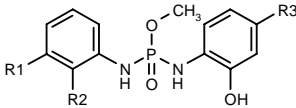
309962

N-(2-Bromophenyl)-*N'*-(4-cyano-2-hydroxyphenyl)phosphorodiamidic acid ethyl ester



C15 H15 Br N3 O3 P; Mol wt: 396.1795

ACTION – IL-8 antagonist with the ability to bind to IL-8α (CXCR1) or IL-8β (CXCR2) receptors, potentially useful for the treatment of IL-8-mediated diseases including psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, multiple sclerosis, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer’s disease, graft-vs.-host disease, allograft rejection, atherosclerosis, gingivitis and osteoporosis. Other compounds from this series of diphenyl phosphonates include the following:



Compound	R1	R2	R3	Formula
309966	H	Br	CN	C ₁₄ H ₁₃ BrN ₃ O ₃ P
309968	H	Cl	CN	C ₁₄ H ₁₃ ClN ₃ O ₃ P
309969	Cl	Cl	CN	C ₁₄ H ₁₂ Cl ₂ N ₃ O ₃ P
309970	H	Br	NO2	C ₁₃ H ₁₃ BrN ₃ O ₅ P
309971	H	Br	Cl	C ₁₃ H ₁₃ BrClN ₂ O ₃ P

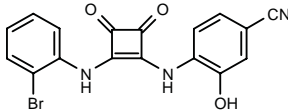
SOURCE – GlaxoSmithKline.

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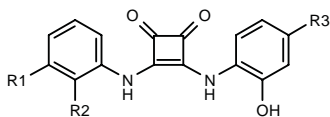
309973

4-[2-(2-Bromophenylamino)-3,4-dioxo-1-cyclobuten-1-ylamino]-3-hydroxybenzonitrile



C17 H10 Br N3 O3; Mol wt: 384.1880

ACTION – IL-8 antagonist with the ability to bind to IL-8α (CXCR1) or IL-8β (CXCR2) receptors, potentially useful for the treatment of IL-8-mediated diseases including psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, multiple sclerosis, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer’s disease, graft-vs.-host disease, allograft rejection, atherosclerosis, gingivitis and osteoporosis. Other compounds from this series of dianilino squarates include the following:



Compound	R1	R2	R3	Formula
309974	H	Cl	CN	C ₁₇ H ₁₀ ClN ₃ O ₃
309975	Cl	Cl	CN	C ₁₇ H ₉ Cl ₂ N ₃ O ₃
309976	H	Br	NO ₂	C ₁₆ H ₁₀ BrN ₃ O ₅
309977	H	Br	Cl	C ₁₆ H ₁₀ BrClN ₂ O ₃

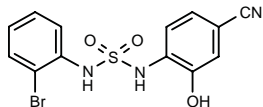
SOURCE – GlaxoSmithKline.

REFERENCES

1. Palovich, M.R. et al. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 0164208.

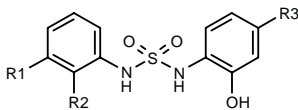
309979

N-(2-Bromophenyl)-N'-(4-cyano-2-hydroxyphenyl)sulfamide



C13 H10 Br N3 O3 S; Mol wt: 368.2100

ACTION – IL-8 antagonist with the ability to bind to IL-8α (CXCR1) or IL-8β (CXCR2) receptors, potentially useful for the treatment of IL-8-mediated diseases including psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, multiple sclerosis, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft-vs.-host disease, allograft rejection, atherosclerosis, gingivitis and osteoporosis. Other compounds from this series of diphenyl sulfamido derivatives include the following:



Compound	R1	R2	R3	Formula
309980	H	Cl	CN	C ₁₃ H ₁₀ ClN ₃ O ₃ S
309981	Cl	Cl	CN	C ₁₃ H ₉ Cl ₂ N ₃ O ₃ S
309983	H	Br	NO ₂	C ₁₂ H ₁₀ BrN ₃ O ₅ S
309984	H	Br	Cl	C ₁₂ H ₁₀ BrClN ₂ O ₃ S

SOURCE – GlaxoSmithKline.

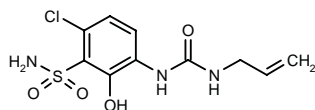
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310187

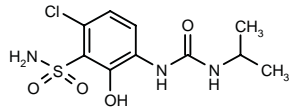
3-(3-Allylureido)-6-chloro-2-hydroxybenzenesulfonamide

N-Allyl-N'-(4-chloro-2-hydroxy-3-sulfamoylphenyl)urea



C10 H12 Cl N3 O4 S; Mol wt: 305.7408

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist, expected to be useful for the treatment of chemokine-mediated diseases including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, stroke, multiple sclerosis, cardiac and renal reperfusion injury, Alzheimer's disease, allograft rejection, malaria, angiogenesis, restenosis, etc. Another specifically claimed compound is:



310188: C10 H14 Cl N3 O4 S

SOURCE – GlaxoSmithKline.

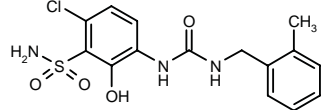
REFERENCES

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310189

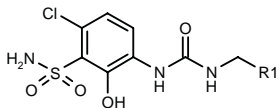
6-Chloro-2-hydroxy-3-[3-(2-methylbenzyl)ureido]-benzenesulfonamide

N-(4-Chloro-2-hydroxy-3-sulfamoylphenyl)-N'-(2-methylbenzyl)urea



C15 H16 Cl N3 O4 S; Mol wt: 369.8274

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist, expected to be useful for the treatment of chemokine-mediated diseases including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, stroke, multiple sclerosis, cardiac and renal reperfusion injury, Alzheimer's disease, allograft rejection, malaria, angiogenesis, restenosis, etc. Other specifically claimed compounds are:



Compound	R1	Formula
310191	Ph	C ₁₄ H ₁₄ ClN ₃ O ₄ S
310192	CH ₂ Ph	C ₁₅ H ₁₆ ClN ₃ O ₄ S

SOURCE – GlaxoSmithKline.

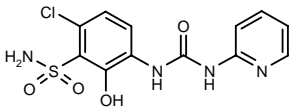
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310193

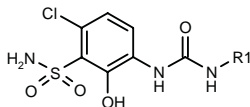
6-Chloro-2-hydroxy-3-[3-(2-pyridyl)ureido]benzenesulfonamide

N-(4-Chloro-2-hydroxy-3-sulfamoylphenyl)-N'-(2-pyridyl)-urea



C₁₂ H₁₁ Cl N₄ O₄ S; Mol wt: 342.7619

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist, expected to be useful for the treatment of chemokine-mediated diseases including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), inflammatory bowel disease, Crohn’s disease, ulcerative colitis, septic shock, stroke, multiple sclerosis, cardiac and renal reperfusion injury, Alzheimer’s disease, allograft rejection, malaria, angiogenesis, restenosis, etc. Other specifically claimed compounds include the following:



Compound	R1	Formula
310194	1-Ph-1,2,3-triazol-5-yl	C ₁₅ H ₁₃ ClN ₆ O ₄ S
310195	1-Me-5-pyrazolyl	C ₁₁ H ₁₂ ClN ₅ O ₄ S
310196	3,5-(Me)2-4-isoxazolyl	C ₁₂ H ₁₃ ClN ₄ O ₅ S
310197	1-oxido-2-Cl-3-Pyr	C ₁₂ H ₁₀ Cl ₂ N ₄ O ₅ S
310198	3-Me-4-isoxazolyl	C ₁₁ H ₁₁ ClN ₄ O ₅ S
310199	5-Me-4-isoxazolyl	C ₁₁ H ₁₁ ClN ₄ O ₅ S

SOURCE – GlaxoSmithKline.

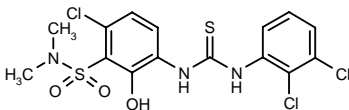
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310200

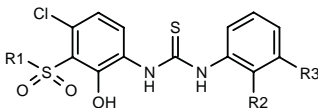
6-Chloro-3-[3-(2,3-dichlorophenyl)thioureido]-2-hydroxy-N,N-dimethylbenzenesulfonamide

N-[4-Chloro-3-(N,N-dimethylsulfamoyl)-2-hydroxyphenyl]-N'-(2,3-dichlorophenyl)thiourea



C₁₅ H₁₄ Cl₃ N₃ O₃ S₂; Mol wt: 454.7846

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist, expected to be useful for the treatment of chemokine-mediated diseases including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), inflammatory bowel disease, Crohn’s disease, ulcerative colitis, septic shock, stroke, multiple sclerosis, cardiac and renal reperfusion injury, Alzheimer’s disease, allograft rejection, malaria, angiogenesis, restenosis, etc. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
310201	2(S)-(MeOCH2)-1-pyrrolidinyl	Br	H	C ₁₉ H ₂₁ BrClN ₃ O ₄ S ₂
310203	2(R)-(MeOCH2)-1-pyrrolidinyl	Br	H	C ₁₉ H ₂₁ BrClN ₃ O ₄ S ₂
310211	2-isoxazolidinyl	Br	H	C ₁₆ H ₁₅ BrClN ₃ O ₄ S ₂
310214	perhydro-1,2-oxazin-2-yl	Br	H	C ₁₇ H ₁₇ BrClN ₃ O ₄ S ₂
310215	perhydro-1,2-oxazin-2-yl	Cl	Cl	C ₁₇ H ₁₆ Cl ₃ N ₃ O ₄ S ₂
310216	4-thiomorpholinyl	Cl	Cl	C ₁₇ H ₁₆ Cl ₃ N ₃ O ₃ S ₃

SOURCE – GlaxoSmithKline.

REFERENCES

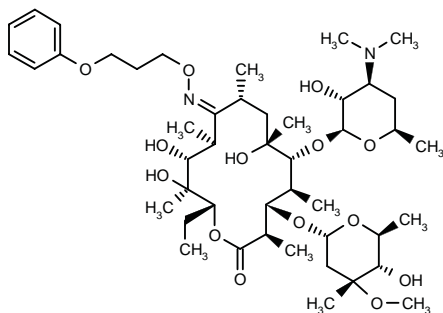
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ANTIINFECTIVE THERAPY

ANTIBIOTICS

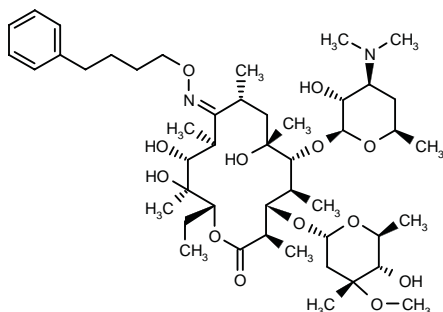
308136

Erythromycin A (*E*)-9-[*O*-(3-phenoxypropyl)oxime]



C46 H78 N2 O14; Mol wt: 883.1222

ACTION – Macrolide antibiotic, an erythromycin A derivative with antibacterial activity against macrolide-susceptible and -resistant *Mycobacterium avium* complex strains (MIC = 1.56-3.13 µg/ml). Compound was also active against *Staphylococcus aureus* with an MIC of 0.78 µg/ml. Another related compound is:



308132: C47 H80 N2 O13

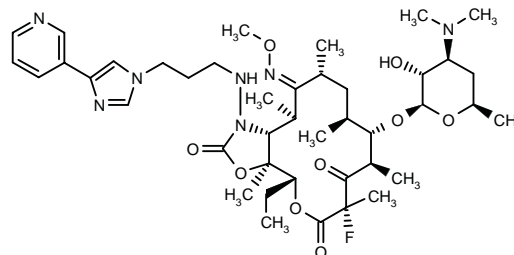
SOURCE – Hokuriku.

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2. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *Erythromycin derivs.* JP 2000351793.
3. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *Erythromycin derivs.* JP 2000351794, WO 0061593.
4. Nishimoto, A. et al. *Studies of macrolide antibiotics I. Synthesis and antibacterial activity of erythromycin A 9-O-substituted oxime ether derivatives against Mycobacterium avium complex.* Chem Pharm Bull 2001, 49(9): 1120.

309609

3-Des(hexopyranosyloxy)-9-deoxy-6,11-dideoxy-2-fluoro-9-(methoxyimino)-3-oxo-11-[2-[3-[4-(3-pyridyl)imidazol-1-yl]propyl]hydrazino]erythromycin A 11-*N*¹,12-*O*-cyclic carbamate



C42 H64 F N7 O9; Mol wt: 830.0056

ACTION – A representative compound from a series of ketolide antibiotics with potential in the treatment of bacterial and protozoal infections.

SOURCE – Pfizer.

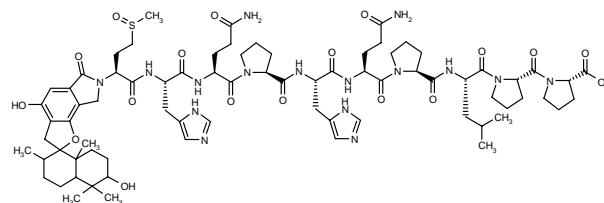
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1. Kaneko, T. et al. (Pfizer Products Inc.) *Ketolide antibiotics.* EP 1132392, JP 2001261694.

MEMNO-PEPTIDE A

309387

N-[2(*S*)-(4,6'-Dihydroxy-2',5',5',8'a-tetramethyl-6-oxo-3,6,7,8-tetrahydro-2*H*-spiro[furo[2,3-*e*]isindole-2,1'-perhydronaphthalen]-7-yl)-4-(methylsulfinyl)butyryl]-L-histidyl-L-glutaminy-L-prolyl-L-histidyl-L-glutaminy-L-prolyl-L-leucyl-L-prolyl-L-proline



C76 H108 N16 O18 S; Mol wt: 1565.8490

ACTION – Peptide isolated from a culture of the micro-organism *Memnoniella echinata* FH2272 (DSM 13195) that activates sarcoplasmic reticulum Ca²⁺-ATPase (SARCA2; EC₅₀ = 6.5 µM using canine cardiac microsomes) and thus exhibits potential in the treatment or prevention of cardiac insufficiency. In addition, it exhibits antimicrobial activity, as demonstrated against *Streptococcus pyogenes*, *Enterococcus faecium*, *Staphylococcus aureus* and *Staphylococcus epidermidis* (MIC values in the range 4- > 64 µg/ml), and is reported to inhibit glucose-6-phosphate translocase, indicating potential in the treatment of diabetes mellitus.

SOURCE – Aventis Pharma.

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TELITHROMYCIN

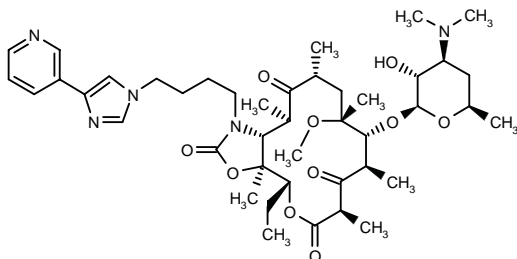
Prop INN

230662

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-*N*-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]amino erythromycin A 11-*N*,12-*O*-cyclic carbamate

(3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyl-11-methoxy-3a,7,9,11,13,15-hexamethyl-1-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-10-[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-xylo-hexopyranosyloxy]octahydro-2*H*-oxacyclotetra-decino[4,3-*d*]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetraone

HMR-3647⁺
RU-66647



C43 H65 N5 O10; Mol wt: 812.0115

ACTION – First-in-class ketolide antibiotic, an inhibitor of bacterial protein synthesis with strong efficacy against upper and lower respiratory tract infections including those caused by resistant pathogens.

INDICATIONS – Treatment of respiratory tract infections including mild or moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis, and tonsillitis or pharyngitis caused by group A β-streptococci.

PRESENTATION – Tablets, 400 mg.

PROPRIETARY NAME – Ketek (DE).

SOURCE – Aventis Pharma.

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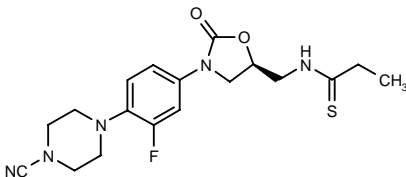
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ANTIBACTERIAL DRUGS

PNU-278605

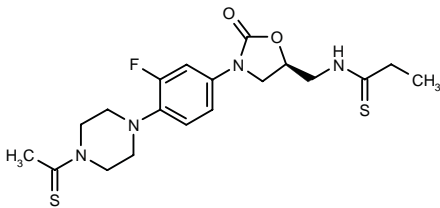
308719

N-[3-[4-(4-Cyanopiperazin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5(S)-ylmethyl]propanethioamide



C18 H22 F N5 O2 S; Mol wt: 391.4688

ACTION – Oxazolidinone antibacterial agent with potent activity against both Gram-positive and Gram-negative bacteria. It was shown to be active *in vitro* against *Staphylococcus aureus* 9213 (MIC = 0.25 µg/ml), *Staphylococcus epidermidis* 30593 (MIC = 0.25 µg/ml), *Enterococcus faecalis* 12712 and 9217 (MIC = 0.25 µg/ml), *Streptococcus pneumoniae* 9912 (MIC = 0.125 µg/ml) and *Moraxella catarrhalis* 30607 (MIC = 1 µg/ml). Another exemplified piperazine-containing oxazolidinone thioamide is:



PNU-276575 [308720]: C19 H25 F N4 O2 S2

SOURCE – Pharmacia.

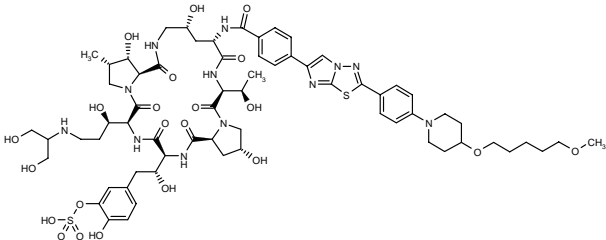
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ANTIFUNGAL AGENTS

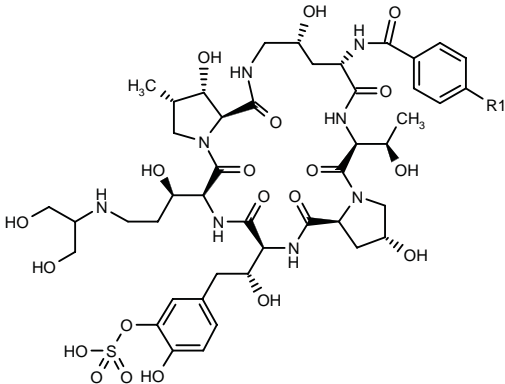
308927

(2*R*,6*S*,9*S*,11*R*,14*aS*,15*S*,16*S*,20*S*,23*S*,25*aS*)-2,11,15-Trihydroxy-6-[1(*R*)-hydroxyethyl]-20-[3-[2-hydroxy-1-(hydroxymethyl)ethylamino]-1(*R*)-hydroxypropyl]-23-[1(*R*)-hydroxy-2-[4-hydroxy-3-(sulfooxy)phenyl]ethyl]-9-[4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl]benzamido]-16-methylperhydrodipyrrolo[2,1-*c*:2',1'-*l*][1,4,7,10,13,16]-hexaazacycloheineicosine-5,8,14,19,22,25-hexaone



C66 H90 N12 O22 S2; Mol wt: 1467.6310

ACTION – Antifungal agent that acts as an inhibitor of β -1,3-glucan synthase and displays an MIC < 0.3 μ g/ml against *Candida albicans* FP-633. It may be particularly useful for the treatment or prevention of *Pneumocystis carinii* pneumonia. Other exemplified cyclic hexapeptide derivatives include the following:



Compound	R1	Formula
308930	cis-5-[4-[4-(4-Me-cyclohexyl)-1-Piz]-Ph]-1,3,4-thiadiazol-2-yl	C ₆₄ H ₈₈ N ₁₂ O ₂₀ S ₂
308931	5-[4-[MeO(CH ₂) ₆ O]-Ph]-3-isoxazolyl	C ₆₁ H ₈₃ N ₉ O ₂₃ S
308933	2-[4-[MeO(CH ₂) ₄ O]-Ph]-imidazo[2,1- <i>b</i>][1,3,4]thiadiazol-6-yl	C ₆₀ H ₇₉ N ₁₁ O ₂₂ S ₂

SOURCE – Fujisawa.

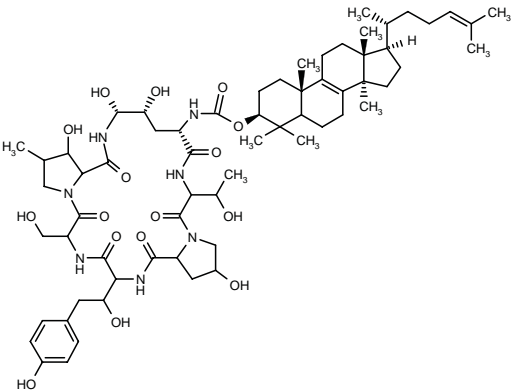
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308945

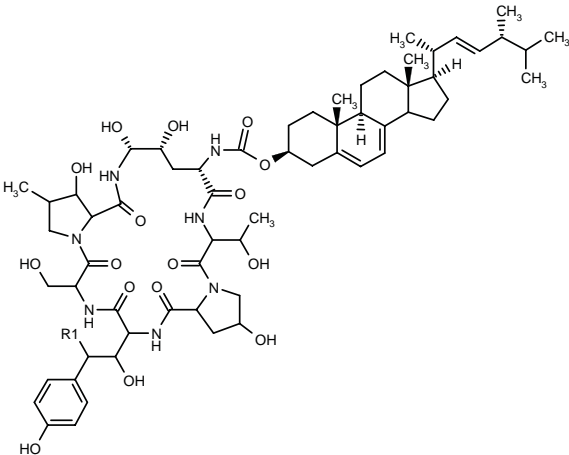
2,11(*R*),12(*R*),15-Tetrahydroxy-6-(1-hydroxyethyl)-23-[1-hydroxy-2-(4-hydroxyphenyl)ethyl]-20-(hydroxymethyl)-9(*S*)-[(3 β)-lanosta-8,24-dien-3-yloxycarbonylamino]-16-methylperhydrodipyrrolo[2,1-*c*:2',1'-*l*][1,4,7,10,13,16]-hexaazaccloeneicosine-5,8,14,19,22,25-hexaone

N-[2,11(*R*),12(*R*),15-Tetrahydroxy-6-(1-hydroxyethyl)-23-[1-hydroxy-2-(4-hydroxyphenyl)ethyl]-20-(hydroxymethyl)-16-methyl-5,8,14,19,22,25-hexaaxoperhydrodipyrrolo-[2,1-*c*:2',1'-*l*][1,4,7,10,13,16]hexaazaccloeneicosine-9(*S*)-yl]carbamic acid (3 β)-lanosta-8,24-dien-3-yl ester



C64 H97 N7 O16; Mol wt: 1220.5030

ACTION – Antifungal echinocandin derivative reported to inhibit glucan synthase from *Candida albicans*. Particularly useful against *C. albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida pseudo-tropicalis*, *Candida parapsilosis*, *Aspergillus fumigatus*, *Aspergillus flavus* and *Cryptococcus neoformans*. Other steroid-containing echinocandin derivatives are:



Compound	R1	Formula
308948	OH	C ₆₂ H ₉₁ N ₇ O ₁₇
308950	H	C ₆₂ H ₉₁ N ₇ O ₁₆

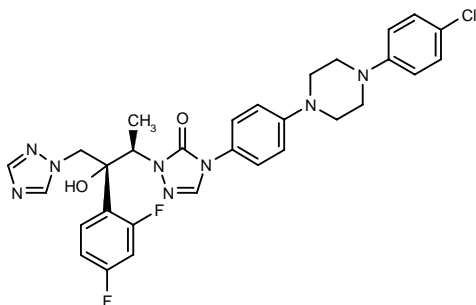
SOURCE – Aventis Pharma.

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310138

4-[4-[4-(4-Chlorophenyl)piperazin-1-yl]phenyl]-2-[(1*R**,2*R**)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3,4-dihydro-2*H*-1,2,4-triazol-3-one



C30 H29 Cl F2 N8 O2; Mol wt: 607.0621

ACTION – Azole antifungal agent reported to exhibit fungicidal activity against *Aspergillus* and *Cryptococcus* species. *In vitro*, compound gave MIC values of < 0.03, 0.12, < 0.03, < 0.03, 0.25, 0.06, < 0.03 and 0.12 µg/ml, respectively, against *Candida albicans* A26, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata* 90030, *Histoplasma capsulatum*, *Cryptococcus neoformans* M106 and *Aspergillus fumigatus* 1008. *In vivo*, it exhibited significant protection against *C. albicans* A26 infections in mice following a single dose of 12.5 mg/kg p.o.

SOURCE – Ranbaxy.

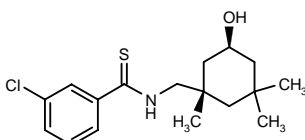
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ANTIVIRAL DRUGS

308004

3-Chloro-*N*-[5(*S**)-hydroxy-1(*S**),3,3-trimethylcyclohexylmethyl]benzenecarbothioamide



C17 H24 Cl N O S; Mol wt: 325.9016

ACTION – Antiviral agent active against influenza A virus subtype H1 (IC₅₀ = 0.02 µg/ml), proven to inhibit influenza A virus-induced red blood cell hemolysis (IC₅₀ = 0.017 µg/ml), indicating that it acts by blocking viral entry into host cells. Low cytotoxicity was seen in uninfected cells (IC₅₀ = 20 µg/ml).

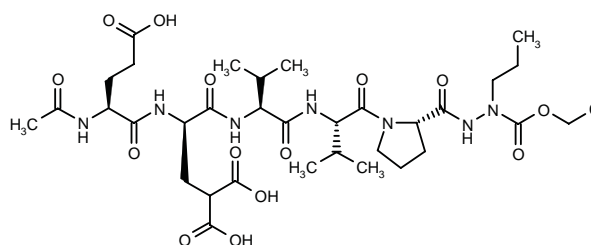
SOURCE – Bristol-Myers Squibb.

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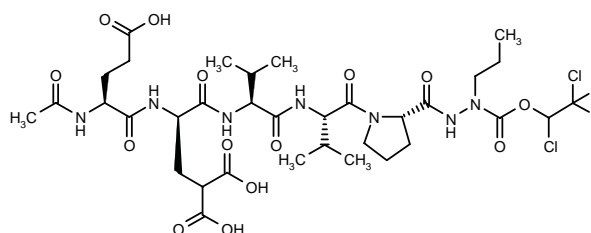
308721

N-Acetyl-L-glutamyl-4-carboxy-D-glutamyl-L-valyl-L-valyl-L-proline *N*'-(chloromethoxycarbonyl)-*N*'-propylhydrazide



C33 H52 Cl N7 O14; Mol wt: 806.2618

ACTION – Inhibitor of hepatitis C virus (HCV) serine proteases, particularly HCV nonstructural protein 3 (NS3; K_i = 0.03 µM), with potential in the treatment of HCV infection. Another exemplified azapeptide is:



308724: C34 H51 Cl4 N7 O14

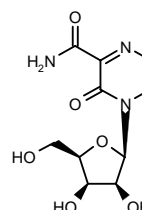
SOURCE – Schering-Plough.

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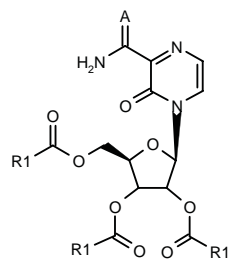
309076

4-(β-D-Lyxofuranosyl)-3-oxo-3,4-dihydropyrazine-2-carboxamide



C10 H13 N3 O6; Mol wt: 271.2277

ACTION – Antiviral agent shown to be active *in vitro* against different strains of influenza virus. It inhibited by 95% the infectivity of influenza virus A/PR/8/34 strain in MDCK cells at 10 mg/ml. Other exemplified pyrazine derivatives are:



Compound	R1	A	Isomer	Formula
309077	Ph	O	β-D-lyxo	C ₃₁ H ₂₈ N ₃ O ₉
309078	Me	NH	β-D-ribo	C ₁₆ H ₂₀ N ₄ O ₈

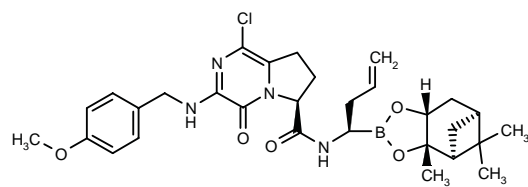
SOURCE – Toyama.

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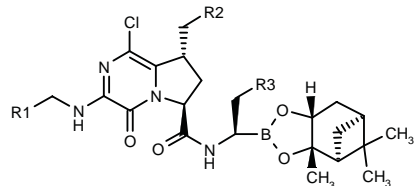
309846

1-Chloro-3-(4-methoxybenzylamino)-4-oxo-*N*-[1(*R*)-[(3*aS*,4*S*,6*S*,7*aR*)-3*a*,5,5-trimethylperhydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]-3-butenyl]-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrazine-6(*S*)-carboxamide

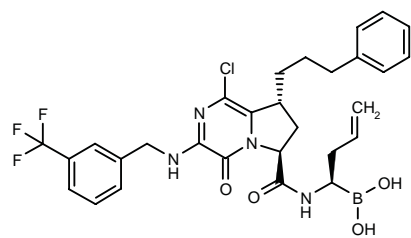


C30 H38 B Cl N4 O5; Mol wt: 580.9172

ACTION – Hepatitis C virus (HCV) NS3 protease inhibitor, potentially useful for the treatment of HCV infection. Other specifically claimed nitrogen-containing fused heterocyclic carboxamides include the following:



Compound	R1	R2	R3	Formula
309847	3-CF3-Ph	CH2CH2Ph	vinyl	C ₃₉ H ₄₅ BClF ₃ N ₄ O ₄
309849	3-Ph-Ph	CH2CH2Ph	vinyl	C ₄₄ H ₅₀ BClN ₄ O ₄
309850	3-CF3-Ph	Ph	vinyl	C ₃₇ H ₄₁ BClF ₃ N ₄ O ₄
309851	3-CF3-Ph	3-MeO-Ph	4-CF3-Ph	C ₄₃ H ₄₄ BClF ₃ N ₄ O ₅
309852	3-CF3-Ph	2-Naph-CH2CH2	H	C ₄₁ H ₄₅ BClF ₃ N ₄ O ₄
309853	i-Pr	CH2CH2Ph	vinyl	C ₃₅ H ₄₈ BClN ₄ O ₄



309854: C29 H31 B Cl F3 N4 O4

SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

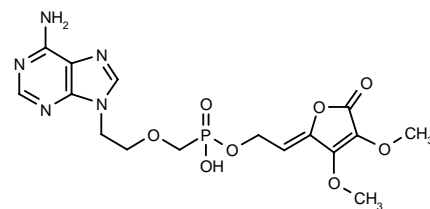
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309987

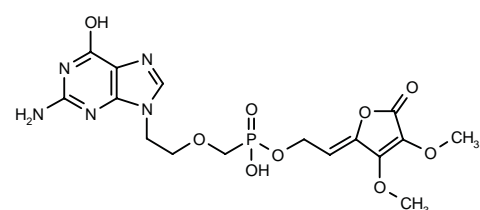
9-[2-[[2(*Z*)-(3,4-Dimethoxy-5-oxo-2,5-dihydrofuran-2-ylidene)ethoxy](hydroxy)phosphoryl-methoxy]ethyl]-adenine

[2-(6-Amino-9*H*-purin-9-yl)ethoxy]methyl]phosphonic acid 2(*Z*)-(3,4-dimethoxy-5-oxo-2,5-dihydrofuran-2-ylidene)-ethyl ester



C16 H20 N5 O8 P; Mol wt: 441.3350

ACTION – Antiviral agent, a butenolide ester prodrug of PMEa with anti-DNA virus and antiretrovirus activity *in vitro*. Compound inhibited the cytopathicity of herpes simplex virus type 1 (HSV-1; IC₅₀ = 3.7 µg/ml), herpes simplex virus type 2 (HSV-2; IC₅₀ = 3.0 µg/ml), thymidine kinase-positive and thymidine kinase-deficient strains of varicella-zoster virus (VZV; IC₅₀ = 2.0 and 2.4 µg/ml, respectively), as well as HIV-1 (IC₅₀ = 1.4 µg/ml), HIV-2 (IC₅₀ = 1.0 µg/ml) and Moloney murine sarcoma virus (MSV; IC₅₀ = 0.93 µg/ml). *In vivo*, doses of 100-250 mg/kg/day i.p. for 6 days gave full protection against HSV-1-induced mortality in mice. Moreover, the prodrug at 10 mg/kg i.p. prevented MSV-induced tumor formation in 60% of infected mice, compared to only 19% protection with PMEa at the same dose level. Another related compound is:



310543: C16 H20 N5 O9 P

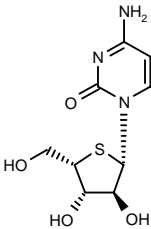
SOURCES – China Medical College, Taichung (TW); Purdue University, West Lafayette, IN (US); Shiraz University, Shiraz (IR); Academia Sinica, Taipei (TW); University of Tehran, Tehran (IR).

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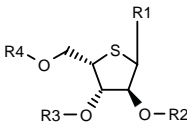
310140

1-(4-Thia-β-L-xylofuranosyl)cytosine



C9 H13 N3 O4 S; Mol wt: 259.2847

ACTION – An inhibitor of DNA replication, potentially useful for the treatment of cancer and viral infections, particularly cytomegalovirus (CMV) infections. *In vitro*, it gave IC₅₀ values of 11.0 and 90 μM, respectively, against human leukemia CCRF-CEM and CNS SNB-7 cancer cells. In addition, compound showed an IC₅₀ of 0.022 μM against CMV, and exhibited a therapeutic index of > 450. Other specifically claimed 4-thia-L-xylofuranosyl nucleosides are:



Compound	R1	R2=R3=R4	Isomer	Formula
310141	2-Cl-adenin-9-yl	H	α-L	C ₁₀ H ₁₂ ClN ₅ O ₃ S
310142	2,6-(NH2)2-purin-9-yl	CH2Ph	α-L	C ₃₁ H ₃₂ N ₆ O ₃ S
310143	guanin-9-yl	H	β-L	C ₁₀ H ₁₃ N ₅ O ₄ S
310144	thymine-1-yl	CH2Ph	L	C ₃₁ H ₃₂ N ₂ O ₅ S
310145	uracil-1-yl	CH2Ph	L	C ₃₀ H ₃₀ N ₂ O ₅ S
310146	thymine-1-yl	H	L	C ₁₀ H ₁₄ N ₂ O ₅ S
310147	uracil-1-yl	H	L	C ₉ H ₁₂ N ₂ O ₅ S
310148	cytosin-1-yl	CH2Ph	L	C ₃₀ H ₃₁ N ₃ O ₄ S
310149	cytosin-1-yl	H	L	C ₉ H ₁₃ N ₃ O ₄ S
310150	2,6-(NH2)2-purin-9-yl	H	α-L	C ₁₀ H ₁₄ N ₆ O ₃ S

SOURCE – Southern Research Institute, Birmingham, AL (US).

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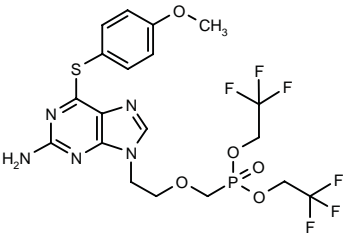
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MCC-478

298405

2-[2-Amino-6-(4-methoxyphenylsulfanyl)-9H-purin-9-yl]ethoxymethylphosphonic acid bis(2,2,2-trifluoroethyl) diester

LY-582563



C19 H20 F6 N5 O5 P S; Mol wt: 575.4250

ACTION – Antiviral agent active against hepatitis B virus (HBV), a PME derivative proven to inhibit duck hepatitis B virus (DHBV; EC₅₀ = 1-2 nM) with 100-fold improved potency compared to lamivudine. In DHBV-infected ducklings, compound at a dose of 2.5 mg/kg/day p.o. was equiactive to lamivudine 12.5 mg/kg/day p.o. at reducing viremia during the first week of treatment (79%), whereas adefovir dipivoxil at a dose of 2.5 mg/kg/day p.o. was less effective (53% reduction); at the end of treatment, compound (0.5 mg/kg/day) reduced viremia by 84%, whereas adefovir dipivoxil (0.5 mg/kg/day) and lamivudine (2.5 mg/kg/day) reduced viremia by only 64 and 44%, respectively. It produced a significant reduction in HBV DNA at the dose of 25 mg/kg/day p.o. in an HBV transgenic mouse model. In chronic woodchuck hepatitis virus (WHV)-infected woodchucks, oral doses of 2.5 and 10 mg/kg/day produced decreases of at least 4 log in mean serum WHV DNA compared to placebo or lamivudine 2.5 mg/kg/day; animals treated with compound at a dose of 2.5 mg/kg/day exhibited sustained reductions in WHV DNA levels for at least 10 weeks after treatment and a dose of 10 mg/kg/day induced undetectable serum WHV DNA levels after 20 weeks in 2 of 3 surviving animals.

SOURCES – Lilly; Mitsubishi Pharma.

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PEGINTERFERON ALFA-2a

261662

40 kD Polyethylene glycol (PEG) covalently linked to interferon alfa-2a

Mono(*N*²,*N*⁶-dicarboxy-L-lysyl)interferon alfa-2a, diesters with polyethylene glycol monomethyl ether

Ro-25-3036⁺

ACTION – Pegylated (polyethylene glycol-modified) human interferon alfa.

INDICATION – Weekly treatment of chronic hepatitis C.

PRESENTATION – Injectable solution, 135 and 180 µg.

PROPRIETARY NAME – PEGASYS (CH).

SOURCE – Roche.

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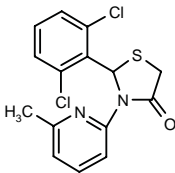
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AIDS MEDICINES

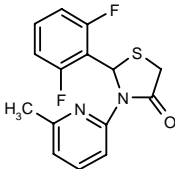
307671

2-(2,6-Dichlorophenyl)-3-(6-methylpyridin-2-yl)thiazolidin-4-one



C15 H12 Cl2 N2 O S; Mol wt: 339.2448

ACTION – Non-nucleoside HIV-1 reverse transcriptase inhibitor (IC₅₀ = 2.24 μM) proven to inhibit the replication of HIV-1 but not HIV-2 in MT cells (EC₅₀ = 0.0082 and > 126 μM, respectively). Compound was not cytotoxic to MT-4 cells and exhibited a selectivity index of 6,470. Another related compound is:



307670: C15 H12 F2 N2 O S

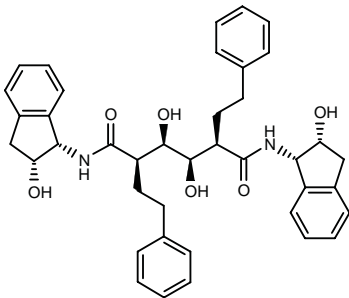
SOURCES – Università degli Studi di Catanzaro, Catanzaro (IT); Università degli Studi di Messina, Messina (IT); Rega Institute for Medical Research, Leuven (BE).

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309137

3(R),4(R)-Dihydroxy-*N*¹,*N*⁶-bis[2(R)-hydroxyindan-1(S)-yl]-2(R),5(R)-bis(2-phenylethyl)hexanediamide



C40 H44 N2 O6; Mol wt: 648.7956

ACTION – Anti-HIV agent, a potent inhibitor of HIV-1 protease (K_i = 1.1 nM) with good antiviral activity in HIV-1-infected cells (EC₅₀ = 93 nM); in the presence of 40% human serum, compound only showed a 4-fold reduction in anti-HIV-1 activity (EC₅₀ = 390 nM).

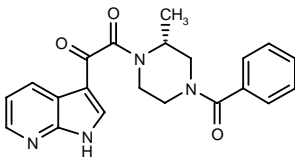
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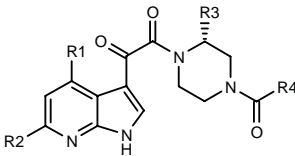
309402

1-[4-Benzoyl-2(R)-methylpiperazin-1-yl]-2-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1,2-dione

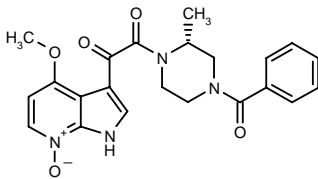


C21 H20 N4 O3; Mol wt: 376.4140

ACTION – Antiviral agent shown to inhibit by > 99% the infectivity of HIV-1 in HeLa CD4 CCR5 cells at < 10 μM, while showing no appreciable cytotoxicity. Other exemplified azaindoles include the following:



Compound	R1	R2	R3	R4	Formula
309403	H	H	H	2-Pyr	C ₁₉ H ₁₇ N ₅ O ₃
309404	H	H	Me	2-Pyr	C ₂₀ H ₁₉ N ₅ O ₃
309405	H	H	Me	5-Br-2-furyl	C ₁₉ H ₁₇ BrN ₄ O ₄
309407	Cl	H	Me	Ph	C ₂₁ H ₁₉ ClN ₄ O ₃
309408	H	Cl	Me	Ph	C ₂₁ H ₁₉ ClN ₄ O ₃
309409	NO2	F	Me	Ph	C ₂₁ H ₁₈ FN ₅ O ₅
309410	H	CN	Me	Ph	C ₂₂ H ₁₉ N ₅ O ₃
309411	OMe	H	Me	Ph	C ₂₂ H ₂₂ N ₄ O ₄
309412	i-PrO	H	Me	Ph	C ₂₄ H ₂₆ N ₄ O ₄



309406: C21 H19 Cl N4 O3

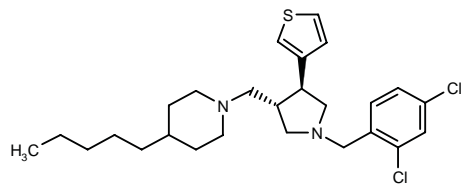
SOURCE – Bristol-Myers Squibb.

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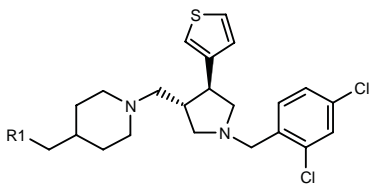
309867

1-[1-(2,4-Dichlorobenzyl)-4 (S)-(3-thienyl)pyrrolidin-3(S)-ylmethyl]-4-pentylpiperidine



C26 H36 Cl2 N2 S; Mol wt: 479.5564

ACTION – Chemokine CCR3 and/or CCR5 receptor modulator, potentially useful for the treatment of HIV infection, as well as inflammatory and autoimmune diseases including asthma, allergic rhinitis, dermatitis, conjunctivitis, atherosclerosis and rheumatoid arthritis. Other specifically claimed pyrrolidine-containing compounds include the following:



Compound	R1	Formula
309869	i-PrO	C ₂₅ H ₃₄ Cl ₂ N ₂ OS
309870	CH(OH)Et	C ₂₅ H ₃₄ Cl ₂ N ₂ OS
309871	i-BuCH(OMe)	C ₂₈ H ₄₀ Cl ₂ N ₂ OS
309873	C(Me)2OPr	C ₂₈ H ₄₀ Cl ₂ N ₂ OS
309874	cycloheptyl-CH(OH)	C ₃₀ H ₄₂ Cl ₂ N ₂ OS
309875	allyl-OC(cyclobutyl)	C ₃₀ H ₄₀ Cl ₂ N ₂ OS
309876	allyl-OCH(4-THP)	C ₃₁ H ₄₂ Cl ₂ N ₂ O ₂ S

SOURCE – Merck & Co.

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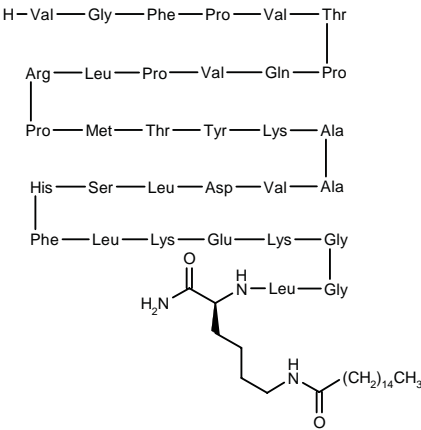
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ANTI-HIV LIPOPEPTIDE VACCINE

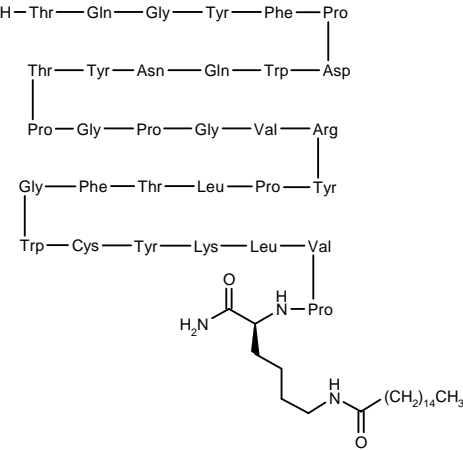
306284

Vaccine consisting of a mixture of 6 lipopeptides which are derived from the HIV-1 proteins NEF, GAG and ENV

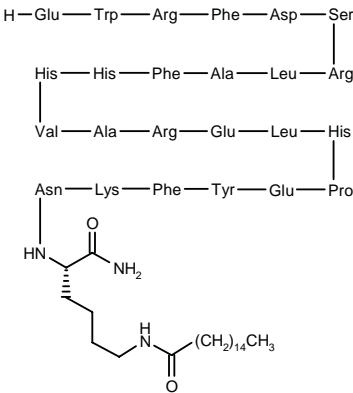
ACTION – AIDS vaccine, a mixture of 6 lipopeptides derived from regulatory or structural HIV-1 proteins (NEF, GAG and ENV) proven to generate cytotoxic and humoral immune responses in a large number of animals. A phase I study in HIV-seronegative volunteers showed that the lipopeptide mixture was well tolerated, with limited local or systemic reactions. An antibody response was seen in 89% of the volunteers following 3 immunizations and it produced reproducible, polyepitopic and strong cytotoxic T-lymphocyte (CTL) responses. The single lipopeptide components of the mixture are:



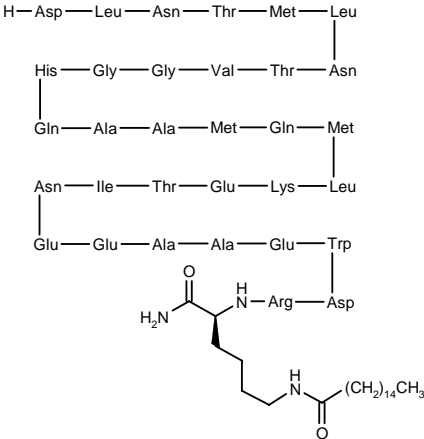
L-N1 [306243]: C185 H302 N44 O43 S



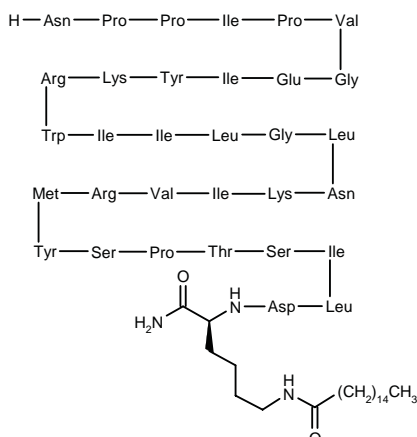
L-N2 [306244]: C198 H283 N43 O45 S



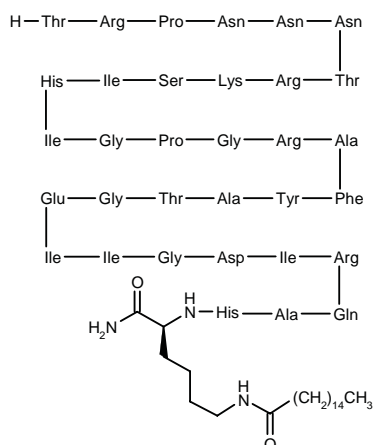
L-N3 [306245]: C165 H245 N45 O37



L-G1 [306246]: C173 H285 N47 O54 S3



L-G2 [306248]: C195 H322 N46 O45 S



L-E [306249]: C180 H297 N57 O48

SOURCES – Aventis Pasteur; CNRS; INSERM, Paris Cedex (FR).

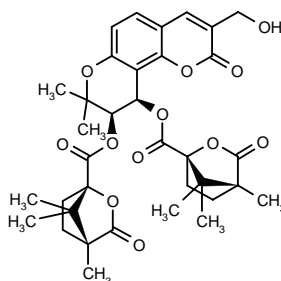
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2. Gahéry-Ségard, H. et al. *Multipepitopic B- and T-cell responses induced in humans by a human immunodeficiency virus type 1 lipopeptide vaccine*. J Virol 2000, 74(4): 1694.
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3-HYDROXYMETHYL-DCK

307997

3-(Hydroxymethyl)-9(*R*),10(*R*)-bis[4(*R*),7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1(*S*)-ylcarbonyloxy]-8,8-dimethyl-2,8,9,10-tetrahydrobenzo[1,2-*b*:3,4-*b'*]dipyran-2-one



C35 H40 O12: Mol wt: 652.6890

ACTION – Anti-HIV agent proven to inhibit HIV-1 replication in acutely infected H9 lymphocytes ($EC_{50} = 0.188$ nM), with low cytotoxicity against uninfected H9 lymphocytes ($IC_{50} = 35.35$ μ M) and an excellent therapeutic index (TI = 188.032).

SOURCE – Panacos.

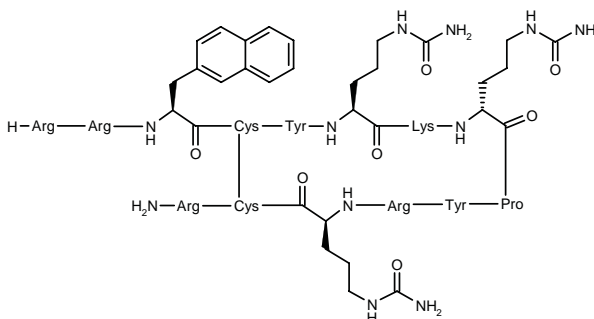
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TC-14012

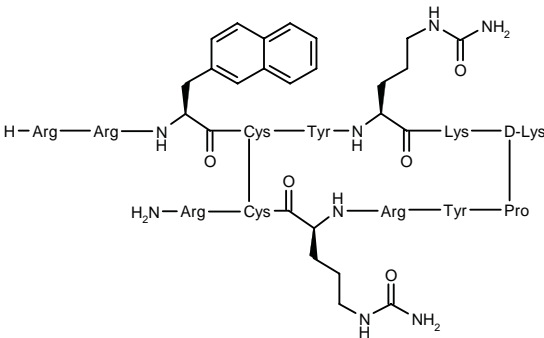
307783

L-Arginyl-L-arginyl-L-3-(2-naphthyl)alanyl-L-cysteinyl-L-tyrosyl-L-citrullinyl-L-lysyl-L-citrullinyl-L-prolyl-L-tyrosyl-L-arginyl-L-citrullinyl-L-cysteinyl-L-argininamide cyclic (4-13)-disulfide



C90 H140 N34 O19 S2: Mol wt: 2066.4470

ACTION – Anti-HIV agent, a chemokine CXCR4 receptor antagonist proven to inhibit HIV-1 entry in CXCR4-expressing cells ($IC_{50} = 19.3$ nM) as well as HIV-1 replication in MT-4 cells ($IC_{50} = 0.4$ nM). Compound exhibited a high selectivity index and complete stability in cat or mouse serum. Another related specific CXCR4 receptor antagonist is:



TN-14003 [307781]: C90 H141 N33 O18 S2

SOURCES – Kagoshima University, Kagoshima (JP); Kyoto University, Kyoto (JP); Tohoku University, Sendai (JP); Tokyo Medical and Dental University, Tokyo (JP).

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TENOFOVIR DISOPROXIL FUMARATE

Prop INN^M, USAN

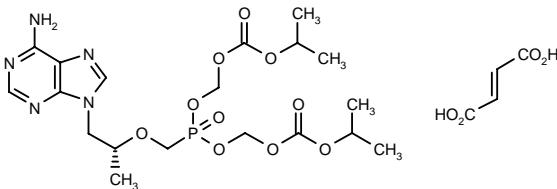
246665

(*R*)-[[2-(6-Amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]-phosphonic acid bis(isopropoxycarbonyloxymethyl) ester fumarate

2-(Adenin-9-yl)-1(*R*)-methylethoxymethylphosphonic acid bis(isopropoxycarbonyloxymethyl) ester fumarate

GS-4331-05

Bis(POC)PMPA⁺



C19 H30 N5 O10 P . C4 H4 O4; Mol wt: 635.5166

ACTION – An ester derivative of tenofovir that is converted *in vivo* to the latter, a nucleotide HIV reverse transcriptase inhibitor.

INDICATION – Treatment of HIV infection in combination with other antiretroviral agents.

PRESENTATION – Tablets, 300 mg, equivalent to 245 mg tenofovir disoproxil.

PROPRIETARY NAME – Viread (US).

SOURCE – Gilead.

RECENT REFERENCES

1. Barditch-Crovo, P. et al. *Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults.* Antimicrob Agents Chemother 2001, 45(10): 2733.

2. Coakley, D. et al. *Tenofovir DF (TDF) 300 mg consistently demonstrates anti-HIV activity regardless of baseline demographic characteristics in antiretroviral (ART)-experienced HIV-1 infected patients.* 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst P56.

3. Cheng, A. et al. *Safety profile of tenofovir DF (TDF) in treatment-experienced patients from randomized, placebo-controlled clinical trials.* 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst P227.

4. Deeks, S.G. et al. *Hydroxyurea does not enhance the anti-HIV activity of low-dose tenofovir disoproxil fumarate.* J Acquir Immune Defic Syndr (JAIDS) 2001, 28(4): 336.

5. Flaherty, J. et al. *A multiple-dose, randomized, crossover, drug interaction study between tenofovir DF and efavirenz, indinavir, or lopinavir/ritonavir.* 1st IAS Conf HIV Pathog Treat (July 8-11, Buenos Aires) 2001, Abst 336.

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7. Kearney, B.P. et al. *Lack of clinically relevant drug-drug interactions between tenofovir DF and efavirenz, indinavir, lamivudine and lopinavir/ritonavir, lamivudine and lopinavir/ritonavir in healthy subjects.* 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst P171.

8. Larder, B.A. et al. *Tenofovir susceptibility among 5000 clinical HIV-1 isolates and 1000 treatment-naïve isolates.* 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst P246.

9. Miller, M.D. et al. *Baseline and week 24 genotypic analyses of HIV from antiretroviral-experienced patients adding tenofovir DF therapy.* 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst O15.

10. Miller, M.D. et al. *Baseline and week 48 final phenotypic analysis of HIV-1 from patients adding tenofovir disoproxil fumarate (TDF) therapy to background ART.* 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 441.

11. Miller, M.D. et al. *HIV-1 RT mutations in patients after 24 weeks of tenofovir disoproxil fumarate (formerly PMPA prodrug) therapy added to stable background ART.* 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 740A.

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13. Palmer, S. et al. *Tenofovir, adefovir, and zidovudine susceptibilities of primary human immunodeficiency virus type 1 isolates with non-B subtypes or nucleoside resistance.* AIDS Res Hum Retroviruses 2001, 17(12): 1167.

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15. Rooney, J.F. et al. *Tenofovir disoproxil fumarate - A novel NRTI in phase III clinical development.* 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst .

16. Schooley, R. et al. *Tenofovir disoproxil fumarate (TDF) for the treatment of antiretroviral experienced patients: A 48 week analysis of a randomized, double blind, placebo-controlled study.* AIDS 2000, 14(Suppl. 4): Abst PL6.3.

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20. Van Gelder, J. et al. *Increased absorption of the antiviral ester prodrug tenofovir disoproxil in rat ileum by inhibiting its intestinal metabolism.* Drug Metab Dispos 2000, 28(12): 1394.

21. *Analysis of mutational patterns associated with resistance to tenofovir and lopinavir/ritonavir.* 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst P352.

22. *Approval of Viread recommended by FDA advisory committee.* DailyDrugNews.com (Daily Essentials) 2001, Oct 17.

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30. *Gilead reports product and pipeline highlights for 2000.* DailyDrugNews.com (Daily Essentials) 2001, Feb 12.

31. *Gilead seeks approval of tenofovir DF for treatment of HIV.* DailyDrugNews.com (Daily Essentials) 2001, May 3.

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34. *Significant milestones achieved by Gilead in antiviral and other programs.* DailyDrugNews.com (Daily Essentials) 2001, July 31.

35. *Tenofovir DF reaches primary efficacy endpoint in phase III trial.* DailyDrugNews.com (Daily Essentials) 2001, Feb 28.

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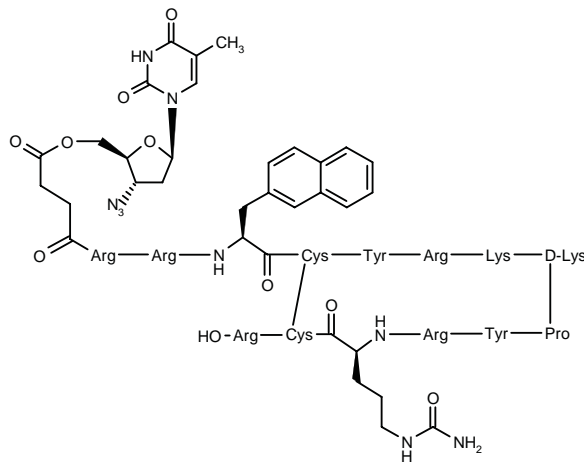
*Drug Data Rep 1997, 019(03): 0257.

TZ-14003

307212

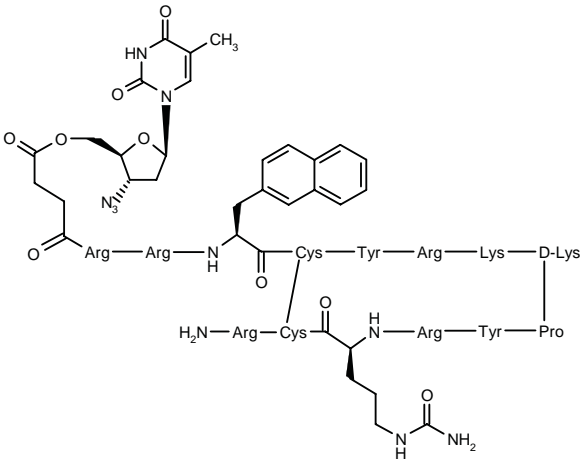
N-[4-(3'-Azido-3'-deoxythymidin-5'-O-yl)-4-oxobuteryl]-L-arginyl-L-arginyl-3-(2-naphthyl)-L-alanyl-L-cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-D-lysyl-L-prolyl-L-tyrosyl-L-arginyl-L-citrullinyl-L-cysteinyl-L-arginine cyclic (4-13)-disulfide

AZT-Suc-T140



C104 H156 N38 O24 S2; Mol wt: 2386.7500

ACTION – Anti-HIV agent, a conjugate of an analogue of the specific chemokine CXCR4 antagonist T-140 and the reverse transcriptase inhibitor zidovudine (AZT), able to efficiently release AZT in aqueous media at pH 7.4. Compound exhibited strong anti-HIV activity *in vitro* 5-fold higher than that of AZT (EC_{50} = 4.6 and 20 nM, respectively). Another related compound is:



TZ-14007 [307044]: C104 H157 N39 O23 S2

SOURCES – Kagoshima University, Kagoshima (JP); Kyoto University, Kyoto (JP);Tokyo Medical and Dental University, Tokyo (JP).

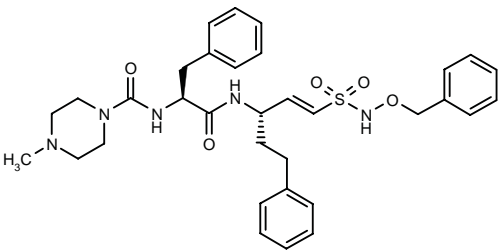
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TREATMENT OF PROTOZOAL DISEASES

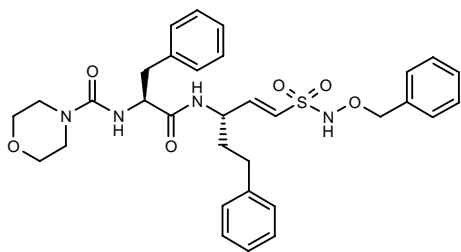
309719

N¹-[3-(N-Benzoyloxysulfamoyl)-1(S)-(2-phenylethyl)-2-propenyl]-N²-(4-methylpiperazin-1-ylcarbonyl)-L-phenylalaninamide



C33 H41 N5 O5 S; Mol wt: 619.7829

ACTION – Antitrypanosomal agent, a potent and irreversible inhibitor of the trypanosomal cysteine protease cruzain, also active against rhodesain, the major cysteine protease isolated from *Trypanosoma brucei rhodesiense*. *In vitro*, in the J744 macrophage cell culture assay system, compound inhibited the growth of *T. cruzi* and prolonged cell survival for > 24 days. Another related compound is:



309717: C32 H38 N4 O6 S

SOURCES – University of California, San Francisco, San Francisco, CA (US); University of Michigan, Ann Arbor, MI (US).

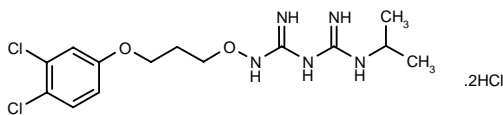
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PS-26

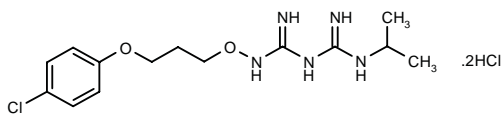
310498

1-[3-(3,4-Dichlorophenoxy)propoxy]-5-isopropylbiguanide dihydrochloride



C14 H21 Cl2 N5 O2 . 2HCl; Mol wt: 435.1807

ACTION – Antimalarial agent, a prodrug of the diamino-triazine WR-99210 active against *Plasmodium berghei* infections in mice, giving an ED₉₀ value < 16 mg/kg p.o. b.i.d. for reducing parasitemia on day 6; complete survival was observed at the dose of 33 mg/kg. p.o. b.i.d. Another related compound is:



PS-33 [310495]: C14 H22 Cl N5 O2 . 2HCl

SOURCE – Jacobus Pharmaceuticals.

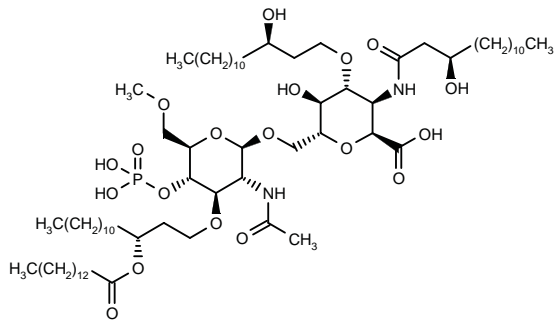
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TREATMENT OF SEPTIC SHOCK

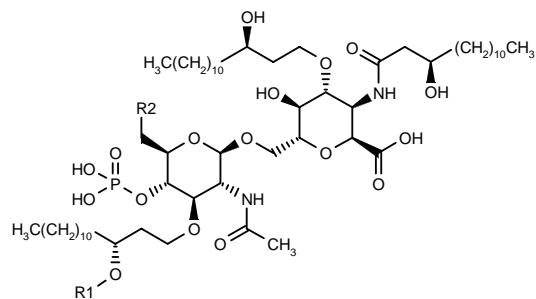
294402

6-*O*-[2-Acetamido-2-deoxy-6-*O*-methyl-4-*O*-phosphono-3-*O*-[3(*R*)-(tetradecanoyloxy)tetradecyl]-β-*D*-glucopyranosyl]-2-deoxy-2-[3(*R*)-hydroxytetradecanamido]-3-*O*-[3(*R*)-hydroxytetradecyl]-*D*-glucopyranosyl-1α-carboxylic acid



C72 H137 N2 O19 P; Mol wt: 1365.8430

ACTION – An inhibitor of lipopolysaccharide (LPS)-induced TNF-α production in human monoblastic U-937 cells (IC₅₀ = 0.61 nM), potentially useful as an immuno-suppressant and for the treatment of septic shock and autoimmune diseases. Other lipid A-type pyran carboxylic acids are:



Compound	R1	R2	Formula
294404	COC13H27	OH	C ₇₁ H ₁₃₅ N ₂ O ₁₉ P
294405	COC13H27	F	C ₇₁ H ₁₃₄ FN ₂ O ₁₈ P
294406	C12H25	OMe	C ₇₀ H ₁₃₅ N ₂ O ₁₈ P
294407	C12H25	OH	C ₆₉ H ₁₃₃ N ₂ O ₁₈ P
294408	C12H25	F	C ₆₉ H ₁₃₂ FN ₂ O ₁₇ P

SOURCE – Sankyo.

REFERENCES

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2. Watanabe, Y. et al. *Synthesis of lipid A type pyran carboxylic acids with ether chains and their biological activities*. Carbohydr Res 2001, 333(3): 203.

DROTRECUGIN ALFA (ACTIVATED)+

275685

Recombinant human activated protein C

LY-203638
rhAPC
Zovant™ (former brand name)

ACTION – Recombinant human activated protein C thought to act by exerting antithrombotic and antiinflam-matoty effects.

INDICATION – Reduction of mortality in adult patients with severe sepsis associated with acute organ dysfunction who have a high risk of death.

PRESENTATION – Vials for i.v. infusion, 5.3 and 20.8 mg of drotrecogin alfa (activated).

PROPRIETARY NAME – Xigris (US).

SOURCE – Lilly.

RECENT REFERENCES

1. Bernard, G.R. et al. *Effect of patients baseline characteristics on the mortality reduction associated with recombinant human activated protein C (rhAPC) in patients with severe sepsis.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A17.

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7. Gelbert, L.M. et al. *Transcript profiling of human endothelial cells defines novel mechanisms by which recombinant human activated protein regulates proinflammatory pathways.* Am J Hum Genet 2000, 67(4, Suppl. 2): Abst 1490.

8. Jackson, C.V. et al. *Pharmacological profile of recombinant, human activated protein C (LY203638) in a canine model of coronary artery thrombosis.* J Pharmacol Exp Ther 2000, 295(3): 967.

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10. Macias, W.L. et al. *Pharmacokinetics of recombinant human activated protein (drotrecogin alfa [activated]) in patients with severe sepsis.* Intensive Care Med 2001, 27(Suppl. 2): Abst 456.

11. Small, D. et al. *Pharmacokinetics of recombinant human activated protein C in patients with severe sepsis: Subgroup analyses.* Chest 2001, 120(4, Suppl.): 157S.

12. Vincent, J.L. et al. *Effect of baseline protein C, antithrombin and IL-6 levels on the mortality reduction associated with recombinant human activated protein C in patients with severe sepsis.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A17.

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14. *Drotrecogin alfa (activated) granted FDA priority review for severe sepsis.* DailyDrugNews.com (Daily Essentials) 2001, March 30.

15. *Enrollment in phase III trial of sepsis treatment stopped by Lilly.* DailyDrugNews.com (Daily Essentials) 2000, June 30.

16. *ESICM highlights: Pharmacokinetics of drotrecogin alfa determined in PROWESS.* DailyDrugNews.com (Daily Essentials) 2001, Oct 18.

17. *FDA extends BLA action date for Lilly's drotrecogin alfa, new brand name accepted.* DailyDrugNews.com (Daily Essentials) 2001, June 15.

18. *First launch for Lilly's Xigris within days of approval.* DailyDrugNews.com (Daily Essentials) 2001, Nov 30.

19. *Lilly details late-stage product pipeline.* DailyDrugNews.com (Daily Essentials) 2000, June 21.

20. *Lilly highlights significant events over last three months; selected late-stage compounds updated.* DailyDrugNews.com (Daily Essentials) 2001, May 7.

21. *Lilly Newsroom - Pipeline and Products.* Lilly Web Site 2001, Jan 23.

22. *Lilly presents detailed update of late- and early-stage product pipeline.* DailyDrugNews.com (Daily Essentials) 2001, Nov 2.

23. *Lilly receives approvable letter from FDA for Xigris.* DailyDrugNews.com (Daily Essentials) 2001, Nov 6.

MONOGRAPH – Sorbera, L.A. et al. *Drotrecogin alfa (activated).* Drugs Fut 2001, 26(5): 0440.

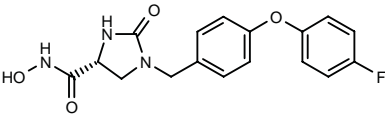
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

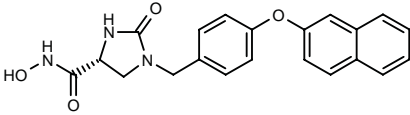
307575

1-[4-(4-Fluorophenoxy)benzyl]-2-oxoimidazolidine-4(R)-carboxyhydroxamic acid



C17 H16 F N3 O4; Mol wt: 345.3284

ACTION – Potent inhibitor of the matrix metalloproteinase MMP-3 (collagenase 3; IC₅₀ = 3 nM) with > 10-fold selectivity over gelatinase A (MMP-2; IC₅₀ = 28 nM) and gelatinase B (MMP-9; IC₅₀ = 62 nM). Potentially useful for the treatment of a variety of diseases including arthritis and cancer. Another related compound is:



307576: C21 H19 N3 O4

SOURCE – Pfizer.

REFERENCES

1. Laird, E.R. and Robinson, R.P. Jr. (Pfizer Products Inc.) *2-Oxo-imidazolidine-4-carboxylic acid hydroxamide cpds. that inhibit matrix metalloproteinases.* EP 1134215, JP 2001261656.

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275685

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Zovant™ (former brand name)

ACTION – Recombinant human activated protein C thought to act by exerting antithrombotic and antiinflam-matoty effects.

INDICATION – Reduction of mortality in adult patients with severe sepsis associated with acute organ dysfunction who have a high risk of death.

PRESENTATION – Vials for i.v. infusion, 5.3 and 20.8 mg of drotrecogin alfa (activated).

PROPRIETARY NAME – Xigris (US).

SOURCE – Lilly.

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18. *First launch for Lilly's Xigris within days of approval.* DailyDrugNews.com (Daily Essentials) 2001, Nov 30.

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20. *Lilly highlights significant events over last three months; selected late-stage compounds updated.* DailyDrugNews.com (Daily Essentials) 2001, May 7.

21. *Lilly Newsroom - Pipeline and Products.* Lilly Web Site 2001, Jan 23.

22. *Lilly presents detailed update of late- and early-stage product pipeline.* DailyDrugNews.com (Daily Essentials) 2001, Nov 2.

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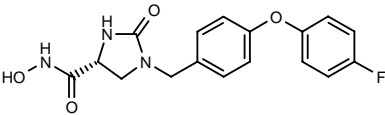
+Drug Data Rep 2001, 023(05): 0487.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

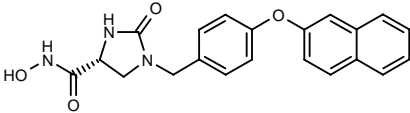
307575

1-[4-(4-Fluorophenoxy)benzyl]-2-oxoimidazolidine-4(R)-carboxyhydroxamic acid



C17 H16 F N3 O4; Mol wt: 345.3284

ACTION – Potent inhibitor of the matrix metalloproteinase MMP-3 (collagenase 3; IC₅₀ = 3 nM) with > 10-fold selectivity over gelatinase A (MMP-2; IC₅₀ = 28 nM) and gelatinase B (MMP-9; IC₅₀ = 62 nM). Potentially useful for the treatment of a variety of diseases including arthritis and cancer. Another related compound is:



307576: C21 H19 N3 O4

SOURCE – Pfizer.

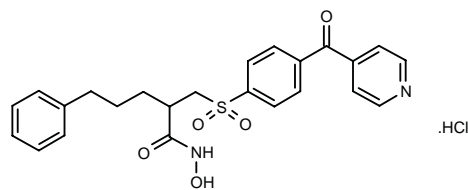
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307648

5-Phenyl-2-[4-(pyridin-4-ylcarbonyl)phenylsulfonylmethyl]pentanohydroxamic acid hydrochloride



C24 H24 N2 O5 S . HCl; Mol wt: 488.9895

ACTION – Potent matrix metalloproteinase (MMP) inhibitor selective for gelatinase A (MMP-2; IC₅₀ = 3 nM), neutrophil collagenase (MMP-8; IC₅₀ = 3 nM) and gelatinase B (MMP-9; IC₅₀ = 15 nM) over interstitial collagenase (MMP-1; IC₅₀ = 10 µM). Compound showed good oral bioavailability in rats, giving significant plasma levels (up to 300 ng/ml) after a dose of 10 mg/kg p.o. It protected rats from adjuvant-induced arthritis (50% protection at 3 mg/kg) and reduced by 80% the growth of B16 melanoma lung metastases in mice at a dose of 30 mg/kg. Potentially useful as an antiarthritic or anti-neoplastic agent.

SOURCE – Celltech Group.

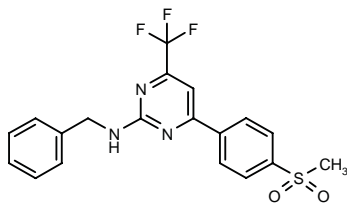
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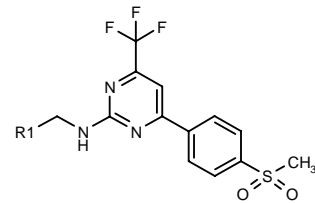
308726

N-Benzyl-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidin-2-amine



C19 H16 F3 N3 O2 S; Mol wt: 407.4144

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor with IC₅₀ values of 0.25 and > 100,000 nM against human COX-2 and COX-1 expressed in COS cells, respectively. Potentially useful for the treatment of acute and chronic pain, fever and inflammation. Other specifically claimed trifluoromethyl-substituted pyrimidine derivatives are:



Compound	R1	Formula
308727	4-Pyr	C ₁₈ H ₁₅ F ₃ N ₄ O ₂ S
308728	3-Pyr	C ₁₈ H ₁₅ F ₃ N ₄ O ₂ S
308730	2-Pyr	C ₁₈ H ₁₅ F ₃ N ₄ O ₂ S
308731	4-MeO-Ph	C ₂₀ H ₁₈ F ₃ N ₃ O ₃ S
308732	4-F-Ph	C ₁₉ H ₁₅ F ₄ N ₃ O ₂ S

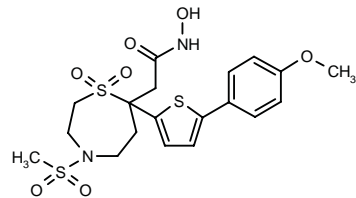
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308986

2-[7-[5-(4-Methoxyphenyl)thien-2-yl]-4-(methylsulfonyl)-1,1-dioxoperhydro-1,4-thiazepin-7-yl]acetohydroxamic acid



C19 H24 N2 O7 S3; Mol wt: 488.6036

ACTION – Inhibitor of matrix metalloproteinases (MMPs) and the production of TNF-α, giving an IC₅₀ of 2.85 nM when tested for inhibition of human MMP-9 (gelatinase B). Potentially useful for the treatment of arthritis, stroke, cancer, tissue ulceration, decubitus ulcer, restenosis, periodontal disease, epidermolysis bullosa, scleritis, psoriasis, AIDS, sepsis and septic shock, among others. A representative compound from a series of thiazepinyl hydroxamic acid derivatives.

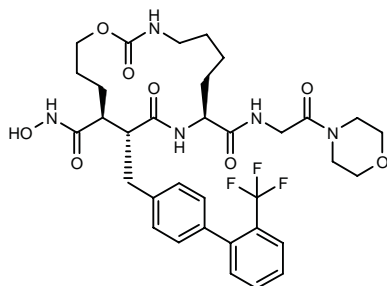
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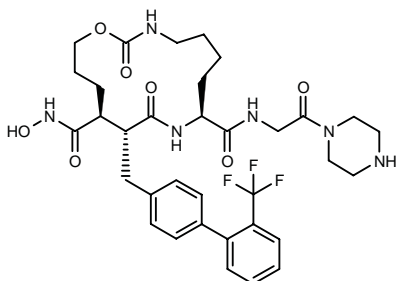
309123

*N*¹²-Hydroxy-*N*⁸-[2-(4-morpholinyl)-2-oxoethyl]-2,10-dioxo-11(*R*)-[2'-(trifluoromethyl)biphenyl-4-ylmethyl]-1-oxa-3,9-diazacyclopentadecane-8(*S*),12(*S*)-dicarboxamide



C34 H42 F3 N5 O8; Mol wt: 705.7268

ACTION – Potent and selective inhibitor of TNF- α -converting enzyme (TACE; $K_i = 2.8$ nM) with > 100-fold selectivity over a panel of 11 matrix metalloproteinases (MMP) and potent cellular activity against lipopolysaccharide-stimulated TNF- α release in human whole blood ($IC_{50} = 70$ nM). Potentially useful for the treatment of autoimmune and inflammatory disorders including rheumatoid arthritis and Crohn's disease. Another related compound is:



309126: C34 H43 F3 N6 O7

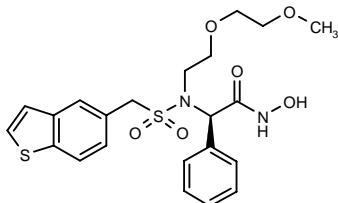
SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

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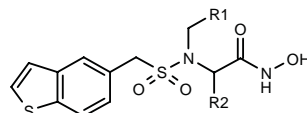
309436

2(*R*)-[*N*-(1-Benzothien-5-ylmethylsulfonyl)-*N*-[2-(2-methoxyethoxy)ethyl]amino]-2-phenylacetohydroxamic acid



C22 H26 N2 O6 S2; Mol wt: 478.5874

ACTION – Agent with the ability to inhibit the formation of soluble human CD23 (sCD23) and the processing of TNF, while having little or no activity against matrix metalloproteinases. It was shown to inhibit the production of sCD23 in RPMI 8866 cell membranes with an $IC_{50} < 1$ μ M compared to an $IC_{50} > 10$ μ M against human recombinant collagenase. Potentially useful for the treatment of autoimmune diseases, inflammation and allergy. Other exemplified sulfonamido-containing hydroxamic acids are:



Compound	R1	R2	Formula
309438	3-Pyr	Ph	C ₂₃ H ₂₁ N ₃ O ₄ S ₂
309439	3-Pyr	(<i>R</i>)-i-Bu	C ₂₁ H ₂₅ N ₃ O ₄ S ₂
309440	2-furyl	(<i>R</i>)-cyclohexyl	C ₂₂ H ₂₆ N ₂ O ₅ S ₂

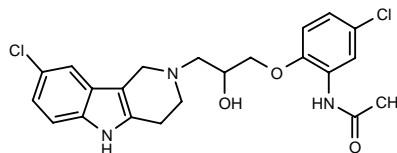
SOURCE – GlaxoSmithKline.

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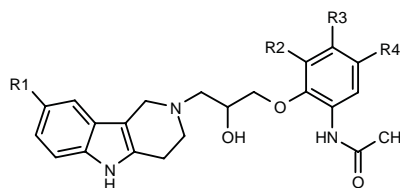
309463

N-[5-Chloro-2-[3-(8-chloro-2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indol-2-yl)-2-hydroxypropoxy]phenyl]acetamide

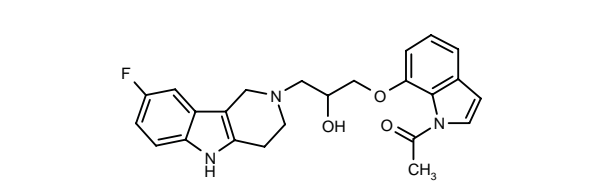


C22 H23 Cl2 N3 O3; Mol wt: 448.3477

ACTION – Modulator of chemokine receptors, particularly the MIP-1 α (CCR1) receptor, with potential in the treatment of inflammatory, autoimmune and respiratory disorders such as rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease and asthma. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	Formula
309464	Cl	H	Me	H	C ₂₃ H ₂₆ ClN ₃ O ₃
309465	Cl	H	H	F	C ₂₂ H ₂₃ ClFN ₃ O ₃
309466	Cl	H	F	H	C ₂₂ H ₂₃ ClFN ₃ O ₃
309467	Cl	H	H	H	C ₂₂ H ₂₄ ClN ₃ O ₃
309468	F	Ac	H	Me	C ₂₆ H ₂₈ FN ₃ O ₄
309470	F	H	F	H	C ₂₂ H ₂₃ F ₂ N ₃ O ₃
309471	F	H	H	H	C ₂₂ H ₂₄ FN ₃ O ₃



309469: C24 H24 F N3 O3

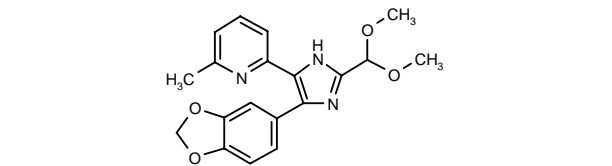
SOURCE – AstraZeneca.

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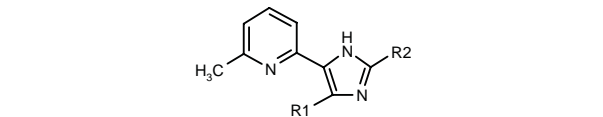
309505

2-[4-(1,3-Benzodioxol-5-yl)-2-(1,1-dimethoxymethyl)-1*H*-imidazol-5-yl]-6-methylpyridine



C19 H19 N3 O4; Mol wt: 353.3761

ACTION – An inhibitor of the tumor growth factor- β (TGF- β) signaling pathway that acts by inhibiting the phosphorylation of smad2 or smad3 by type I or activin-like kinase ALK5 receptor. Potentially useful for the treatment of ALK5-mediated disorders including acute and chronic renal diseases, wound healing, arthritis, osteoporosis, congestive heart failure, ulcers, ocular disorders, diabetic nephropathy, Alzheimer's disease, atherosclerosis and restenosis. Other exemplified imidazole-substituted pyridines are:



Compound	R1	R2	Formula
309506	6-quinoxaliny	Et	C ₁₉ H ₁₇ N ₅
309507	4-MeO-Ph	Me	C ₁₇ H ₁₇ N ₃ O
309508	3,4-dihydro-2 <i>H</i> -1,4-benzoxazin-7-yl	<i>t</i> -Bu	C ₂₁ H ₂₄ N ₄ O
309509	6-benzoxazolyl	<i>t</i> -Bu	C ₂₀ H ₂₀ N ₄ O
309510	2,1,3-benzoxadiazol-5-yl	Me	C ₁₆ H ₁₃ N ₅ O
309511	6-benzothiazolyl	Me	C ₁₇ H ₁₄ N ₄ S

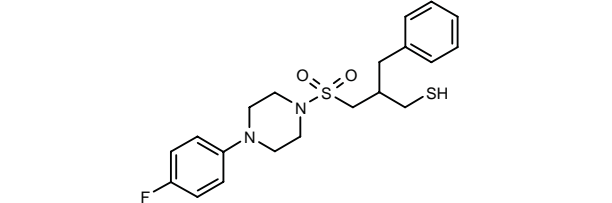
SOURCE – GlaxoSmithKline.

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309537

2-Benzyl-3-[4-(4-fluorophenyl)piperazin-1-ylsulfonyl]-propane-1-thiol



C20 H25 F N2 O2 S2; Mol wt: 408.5595

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly collagenase 3 (MMP-13), with potential for the treatment of arthritis, atherosclerosis and chronic obstructive pulmonary disease. A specifically claimed compound from a series of arylpiperazines.

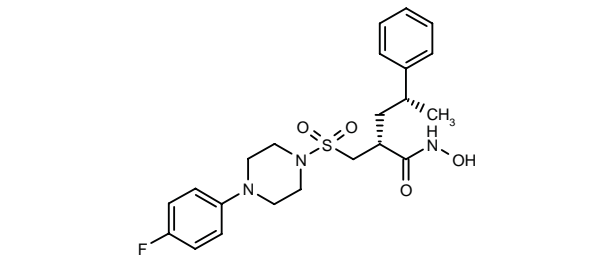
SOURCE – AstraZeneca.

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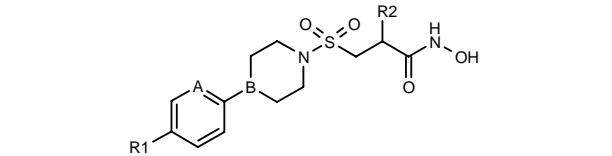
309538

(2*R**,4*R**)-2-[4-(4-Fluorophenyl)piperazin-1-ylsulfonyl-methyl]-4-phenylpentanohydroxamic acid



C22 H28 F N3 O4 S; Mol wt: 449.5442

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly MMP-13 (collagenase 3), potentially useful for the treatment of arthritis, atherosclerosis and chronic obstructive pulmonary disease. Other specifically claimed compounds within this series of arylpiperidines and arylpiperazines are:



Compound	R1	R2	A	B	Formula
309539	Cl	Ph	N	N	C ₁₈ H ₂₁ ClN ₄ O ₄ S
309540	F	CH ₂ CH ₂ Ph	CH	N	C ₂₁ H ₂₆ FN ₃ O ₄ S
309541	F	CH ₂ Ph	CH	N	C ₂₀ H ₂₄ FN ₃ O ₄ S
309542	F	CH ₂ Ph	CH	CH	C ₂₁ H ₂₅ FN ₂ O ₄ S

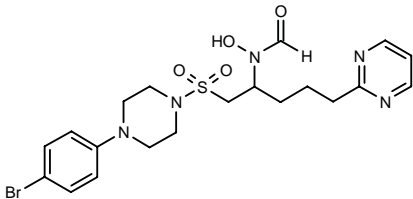
SOURCE – AstraZeneca.

REFERENCES

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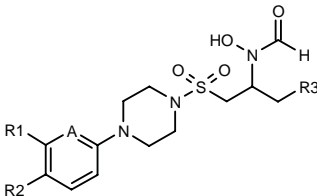
309543

N-[1-[4-(4-Bromophenyl)piperazin-1-ylsulfonylmethyl]-4-(2-pyrimidinyl)butyl]-*N*-hydroxyformamide



C20 H26 Br N5 O4 S; Mol wt: 512.4264

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly collagenase 3 (MMP-13), with potential for the treatment of arthritis, atherosclerosis and chronic obstructive pulmonary disease. Other specifically claimed compounds from this series of piperidine- and piperazine-substituted *N*-hydroxyformamides include the following:



Compound	R1	R2	R3	A	Isomer	Formula
309544	H	Br	2-Pyr-CH2CH2	N	S	C ₂₀ H ₂₆ BrN ₅ O ₄ S
309545	H	F	2-pyrimidinyl-CH2CH2	CH	S	C ₂₀ H ₂₆ FN ₅ O ₄ S
309547	H	Cl	2-pyrimidinyl-CH2	N	R	C ₁₈ H ₂₂ ClN ₆ O ₄ S
309549	H	CF3	2-pyrimidinyl-CH2	N	R	C ₁₉ H ₂₃ F ₃ N ₆ O ₄ S
309550	H	CF3	2-pyrimidinyl-CH2CH2	N	S	C ₂₀ H ₂₅ F ₃ N ₆ O ₄ S
309552	Cl	Cl	5-F-2-pyrimidinyl-CH(Me)	CH	1R*,3R*	C ₂₀ H ₂₄ Cl ₂ FN ₅ O ₄ S
309554	H	Cl	5-Cl-3-Pyr-CH2	CH		C ₂₀ H ₂₄ ClFN ₄ O ₄ S

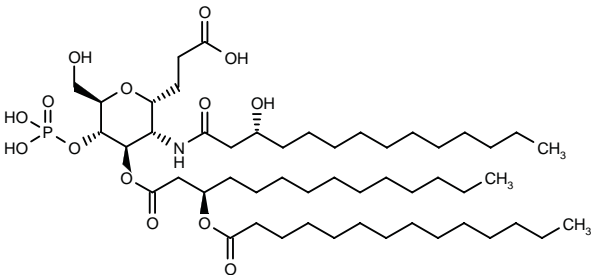
SOURCE – AstraZeneca.

REFERENCES

1. Barlaam, B.C. et al. (AstraZeneca AB;AstraZeneca plc) *Piperidine- and piperazine substd. N-hydroxyformamides as inhibitors of metalloproteinases*. WO 0162742.

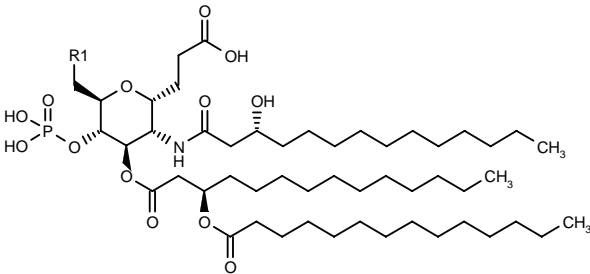
309667

4,8-Anhydro-2,3,5-trideoxy-5-[3(*R*)-hydroxytetradecan-amido]-7-*O*-phosphono-6-*O*-[3(*R*)-(tetradecanoyloxy)-tetradecanoyl]-*D*-glycero-*D*-ido-nononic acid



C51 H96 N O14 P; Mol wt: 978.2864

ACTION – An inhibitor of macrophage activity, expected to be useful for the treatment of inflammation, autoimmune diseases and sepsis. Other exemplified 4-phosphono-glucosamine analogues are:



Compound	R1	Formula
309668	OMe	C ₆₂ H ₉₈ NO ₁₄ P
309670	F	C ₅₇ H ₉₅ FNO ₁₃ P

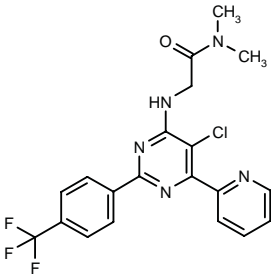
SOURCE – Sankyo.

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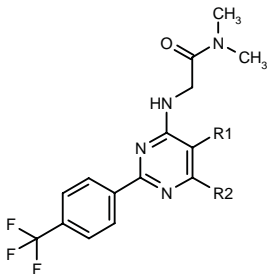
309674

2-[5-Chloro-6-(2-pyridyl)-2-[4-(trifluoromethyl)phenyl]-pyrimidin-4-ylamino]-*N,N*-dimethylacetamide



C20 H17 Cl F3 N5 O; Mol wt: 435.8353

ACTION – Agent for treatment of rheumatoid arthritis and autoimmune inflammatory diseases including multiple sclerosis, systemic lupus erythematosus and Sjögren’s syndrome. The compound displayed an inhibitory rate of 97.9% in a mouse model of collagen-induced arthritis at an oral dose of 10 mg/kg. Other exemplified 4-(trifluoromethyl)phenyl-substituted pyrimidines are:

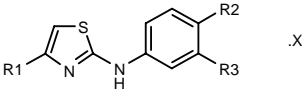


Compound	R1	R2	Formula
309675	Br	2-Pyr	C ₂₀ H ₁₇ BrF ₃ N ₅ O
309677	Cl	3-Pyr	C ₂₀ H ₁₇ ClF ₃ N ₅ O
309678	Br	3-Pyr	C ₂₀ H ₁₇ BrF ₃ N ₅ O
309680	Cl	4-Pyr	C ₂₀ H ₁₇ ClF ₃ N ₅ O

SOURCE – Dainippon Pharmaceutical.

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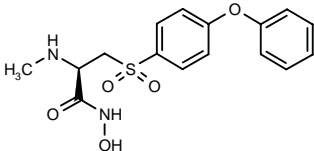
1. Murata, A. et al. (Dainippon Pharmaceutical Co., Ltd.) *6-Heteroaryl-2-(4-trifluoromethylphenyl)pyrimidine derivs. and medicinal compsns. containing them.* JP 2001220389.



Compound	R1	R2	R3	X	Formula
309726	imidazo[1,2-a]pyridin-3-yl	Me	H	HCl	C ₁₇ H ₁₄ N ₄ S.HCl
309727	5-pyrimidinyl	H	CF3		C ₁₄ H ₉ F ₃ N ₄ S
309728	imidazo[1,2-a]pyridin-3-yl	H	Br		C ₁₆ H ₁₁ BrN ₄ S

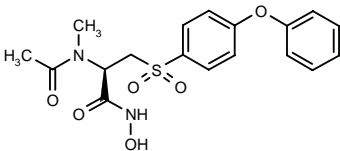
309704

2(R)-(Methylamino)-3-(4-phenoxyphenylsulfonyl)-propionohydroxamic acid



C16 H18 N2 O5 S; Mol wt: 350.3932

ACTION – Potent matrix metalloproteinase (MMP) inhibitor selective for collagenase 3 (MMP-13; IC₅₀ = 0.4 nM) over interstitial collagenase (MMP-1; IC₅₀ = 440 nM). Compound was well absorbed in rats after oral administration and showed a C_{max} of 6.66 µg/ml, with levels of 0.049 µg/ml at 6 h following a dose of 20 mg/kg. Potentially useful for the treatment of arthritis or cancer. Another related compound is:



309705: C18 H20 N2 O6 S

SOURCE – Pharmacia.

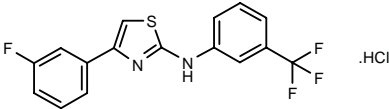
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309725

4-(3-Fluorophenyl)-N-[3-(trifluoromethyl)phenyl]thiazol-2-amine hydrochloride



C16 H10 F4 N2 S . HCl; Mol wt: 374.7879

ACTION – Adenosine A₃ receptor antagonist reported to inhibit the production of IL-12 and TNF-α by 72 and 59%, respectively, at 0.1 µM. Potentially useful for the treatment of inflammatory and autoimmune diseases, particularly rheumatoid arthritis, Crohn's disease, inflammatory bowel disease and colitis. Other exemplified 2,4-disubstituted thiazole derivatives include the following:

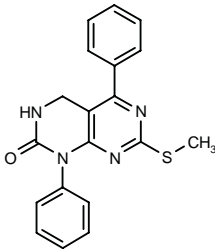
SOURCE – Janssen.

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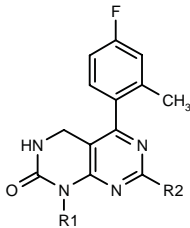
309757

7-(Methylsulfonyl)-1,5-diphenyl-1,2,3,4-tetrahydro-pyrimido[4,5-d]pyrimidin-2-one



C19 H16 N4 O S; Mol wt: 348.4284

ACTION – Agent with the ability to inhibit the production of the proinflammatory proteins TNF, IL-1, IL-6, IL-8 and COX-2 through inhibition of CSBP/p38 kinase. Potentially useful in the treatment of a broad range of inflammatory and other disorders including arthritis, septic shock, meningitis, ischemic and hemorrhagic stroke, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, osteoporosis, restenosis, congestive heart failure, chronic renal failure, diabetes, allograft rejection, inflammatory bowel disease, neurodegeneration or viral infections. Other specifically claimed pyrimido-[4,5-d]pyrimidinone compounds include the following:



Compound	R1	R2	Formula
309759	(R)-CH(Me)Ph	SMe	C ₂₂ H ₂₁ FN ₄ OS
309760	2,6-(F)2-Ph	1-Me-2-imidazolyl	C ₂₃ H ₁₇ F ₃ N ₆ O
309761	2,6-(F)2-Ph	1-Piz	C ₂₃ H ₂₁ F ₃ N ₆ O
309762	2,6-(F)2-Ph	4-morpholinyl	C ₂₃ H ₂₀ F ₃ N ₅ O ₂
309763	2,6-(F)2-Ph	N(Me)2	C ₂₁ H ₁₈ F ₃ N ₆ O
309764	2-F-Ph	SMe	C ₂₀ H ₁₆ F ₂ N ₄ OS
309766	2,6-(F)2-Ph	NHCH2CH(OH)CH2OH	C ₂₂ H ₂₀ F ₃ N ₅ O ₃

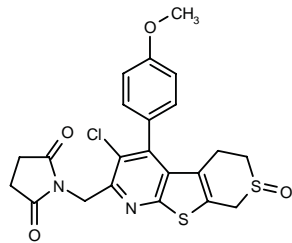
SOURCE – GlaxoSmithKline.

REFERENCES

1. Adams, J.L. et al. (SmithKline Beecham Corp.) *1,5-Disubstd.-3,4-dihydro-1H-pyrimido[4,5-d]pyrimidin-2-one cpds. and their use in treating CSBP/p38 kinase mediated diseases.* WO 0164679.

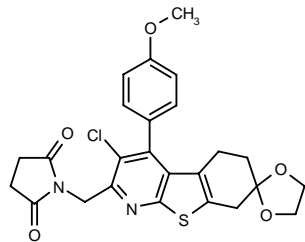
309767

1-[3-Chloro-4-(4-methoxyphenyl)-7-oxo-6,8-dihydro-5H-thiopyrano[4',3':4,5]thieno[2,3-b]pyridin-2-ylmethyl]pyrrolidine-2,5-dione



C22 H19 Cl N2 O4 S2; Mol wt: 474.9871

ACTION – Antiinflammatory and antiarthritic agent and bone resorption inhibitor proven to inhibit paw swelling by 88% in a rat adjuvant arthritis model at 3.13 mg/kg/day p.o. x 14 days. Another exemplified compound from this series of thienopyridine derivatives is:



309768: C25 H23 Cl N2 O5 S

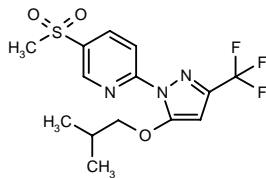
SOURCE – Takeda.

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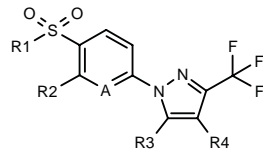
309780

2-[5-Isobutoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-(methylsulfonyl)pyridine



C14 H16 F3 N3 O3 S; Mol wt: 363.3584

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor, potentially useful in the treatment of a wide variety of inflammatory and COX-2-mediated conditions including arthritis, fever, inflammatory bowel disease, acute respiratory distress syndrome, chronic obstructive pulmonary disease, asthma, bronchitis, Alzheimer’s disease, allergies, cancer, tissue ulceration, gastritis, etc. Other specifically claimed pyrazole ether derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
309781	NH2	F	i-PrO	H	CH	C ₁₃ H ₁₃ F ₄ N ₃ O ₃ S
309782	Me	H	cyclohexyl-S	CHO	N	C ₁₇ H ₁₈ F ₃ N ₃ O ₃ S ₂
309783	Me	H	cyclopentyl-NH	CHO	N	C ₁₆ H ₁₇ F ₃ N ₄ O ₃ S
309784	Me	H	cyclopentyl-NH	CH=NOMe	N	C ₁₇ H ₂₀ F ₃ N ₅ O ₃ S
309785	Me	H	cyclohexyl-CH2NH	CN	N	C ₁₈ H ₂₀ F ₃ N ₅ O ₂ S
309786	Me	H	i-PrNH	CHO	N	C ₁₄ H ₁₅ F ₃ N ₄ O ₃ S

SOURCE – Pfizer.

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ANAKINRA
Rec INN, USAN

184798

Recombinant human interleukin-1 receptor antagonist

A recombinant nonglycosylated human interleukin-1 receptor antagonist isolated from human monocytes and cloned and expressed in *Escherichia coli*

N²-L-Methionylinterleukin 1 receptor antagonist (human isoform x reduced)

IL-1ra
rhIL-1ra
Antril⁺ (former brand name)

ACTION – Recombinant IL-1 receptor antagonist.

INDICATION – For the reduction of signs and symptoms of moderately to severely active rheumatoid arthritis in adult patients who have failed one or more disease-modifying antirheumatic drugs (DMARDs).

PRESENTATION – Single-use, prefilled glass syringes (1 ml) containing 100 mg of anakinra.

PROPRIETARY NAME – Kineret (US).

SOURCE – Amgen.

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38. Amgen reviews third quarter developments. DailyDrugNews.com (Daily Essentials) 2000, Nov 17.

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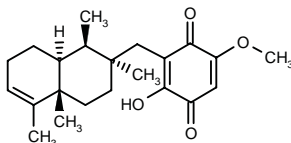
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*Drug Data Rep 1992, 014(09): 0762.

BOLINAQUINONE

308300

(-)-2-Hydroxy-5-methoxy-3-[(1*R**,2*R**,4*aS**,8*aS**)-1,2,4*a*,5-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydro-naphthalen-2-ylmethyl]-1,4-benzoquinone



C22 H30 O4; Mol wt: 358.4750

ACTION – Potential antiinflammatory agent, a sesquiterpene metabolite of the Philippine sponge *Dysidea* sp. Compound was a potent but nonselective inhibitor of human synovial secretory phospholipase A₂ (sPLA₂; IC₅₀ = 0.2, 0.1 and 0.4 μM against human synovial, bee venom and porcine pancreatic enzyme, respectively) and it also inhibited human neutrophil elastase degranulation (IC₅₀ = 5.2 μM), with no significant cytotoxicity against human neutrophils at up to 10 μM. *In vivo*, compound showed antiinflammatory activity in the mouse carrageenan-induced paw edema (51.5% reduction in edema at 12.5 mg/kg p.o.) and TPA-induced ear edema models (ED₅₀ = 76.7 μg/ear).

SOURCES – Università di Napoli Federico II, Napoli (IT); Universidad de Valencia, Valencia (ES).

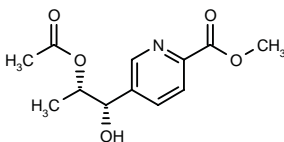
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CJ-14897

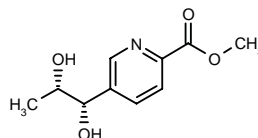
309093

5-[2(*S*)-Acetoxy-1(*S*)-hydroxypropyl]pyridine-2-carboxylic acid methyl ester



C12 H15 N O5; Mol wt: 253.2525

ACTION – Potential antiinflammatory agent extracted from the fermentation broth of the basidiomycete *Marasmiellus* sp. CL21624, proven to inhibit lipopoly-saccharide-stimulated IL-1β and TNF-α production in human whole blood with respective IC₅₀ values of 0.059 and 0.59 μM. Compound did not inhibit leucine uptake at up to 180 μM, indicating that its activity is not due to inhibition of protein synthesis. Another related compound is:



CJ-14877* [278329]: C10 H13 N O4

SOURCE – Pfizer.

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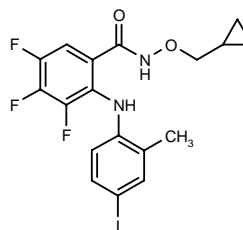
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*Identified compound **278329** Drug Data Rep 1999, 021(08): 0728.

PD-198306

311005

N-(Cyclopropylmethoxy)-3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)benzamide



C18 H16 F3 I N2 O2; Mol wt: 476.2304

ACTION – Antiarthritic agent, a highly selective ERK1/2 inhibitor proven to significantly decrease the size and grade of microscopic cartilage lesions, as well as the severity of cartilage lesions and synovial inflammation, in a rabbit model of experimental osteoarthritis at doses of 10 or 30 mg/kg/day p.o. In these osteoarthritic animals, compound produced a decrease in chondrocytes positive for phospho-ERK1/2 and interstitial collagenase (matrix metalloproteinase MMP-1).

SOURCE – Pfizer.

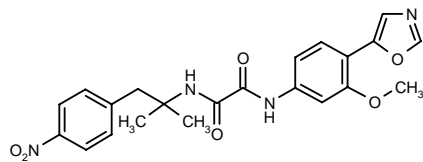
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IMMUNOMODULATING AGENTS

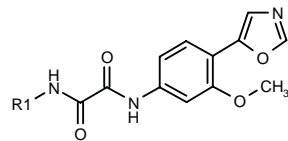
309261

*N*¹-[1,1-Dimethyl-2-(4-nitrophenyl)ethyl]-*N*²-[3-methoxy-4-(5-oxazolyl)phenyl]oxamide



C22 H22 N4 O6; Mol wt: 438.4378

ACTION – An inhibitor of IMP dehydrogenase (IMPDH; IC₅₀ = 0.010 μM) with potential as an immunosuppressant, as well as for the treatment of cancer, microbial and parasitic infections, inflammation and vascular hyperproliferation. Other exemplified oxamides include the following:



Compound	R1	Formula
309262	3-(PhCONHCH2)-Ph	C ₂₆ H ₂₂ N ₄ O ₅
309263	C(Me)2CH2Ph	C ₂₂ H ₂₃ N ₃ O ₄
309264	3-(PhOCONHCH2)-Ph	C ₂₆ H ₂₂ N ₄ O ₆

SOURCE – Roche.

REFERENCES

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ACTION – Antineoplastic agent, an organotin compound with *in vitro* cytotoxic activity against a panel of human cancer cells including Jurkat and MOLT-4 leukemia cells (IC₅₀ = 0.77 and 2.99 μM, respectively), small cell lung carcinoma NCI-N592 and non-small cell lung carcinoma A549 (2.23 and 2.94 μM, respectively), colon adenocarcinoma HCT 116 and HCT-8 (IC₅₀ = 3.24 and 4.69 μM, respectively), breast adenocarcinoma MDA-MB-231 and MCF-7 (IC₅₀ = 6.05 and 7.85 μM, respectively), and ovarian carcinoma SW 626, IGROV1 and OVCAR-3 cells (IC₅₀ = 0.9, 0.7 and 0.5 μM). *In vivo* in mice bearing P388 leukemia, compound at doses of 3.5-14 mg/kg i.p. induced a dose-dependent and statistically significant reduction in tumor growth of 25-46%. When administered to mice bearing B16 melanoma or 3LL Lewis lung carcinoma as repeated oral doses of 21 mg/kg, significant inhibition (70 and 90%, respectively) of tumor volume was found. No severe toxicity was seen at up to 14 mg/kg i.p., whereas the dose of 21 mg/kg i.p. produced important histological alterations and severe body weight loss.

SOURCES – Università degli Studi di Genova, Genova (IT); Istituto Nazionale Ricerca sul Cancro, Genova (IT).

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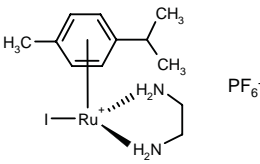
4. Cagnolli, M. et al. *Synthesis and biological activity of gold and tin compounds in ovarian cancer cells*. Anti-Cancer Drugs 1998, 9(7): 603.

5. Novelli, F. et al. *Triorganotin compounds as antimicrobial agents*. Farmaco 1999, 54(4): 237.

RM-121

296240

(1,2-Ethanediamine-κ*N*,κ*N*')iodo[(1,2,3,4,5,6-η)-1-isopropyl-4-methylbenzene]ruthenium(II) hexafluorophosphate



C12 H22 F6 I N2 P Ru; Mol wt: 567.2518

ACTION – Ruthenium(II) organometallic complex proven to inhibit the growth of human ovarian cancer A2780 cells (IC₅₀ = 8 μM) with potency similar to carboplatin (IC₅₀ = 6 μM). Compound does not inhibit topoisomerases but binds strongly and selectively to guanine bases on DNA oligonucleotides to form monofunctional adducts. Other related compounds are:

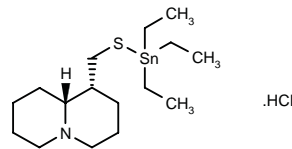
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

IST-FS-29

311056

(1*R*,9*aR*)-1-(Triethylstannylsulfanylmethyl)perhydroquinolizine hydrochloride

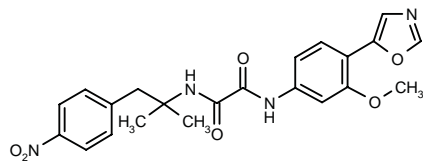


C16 H33 N S Sn . HCl; Mol wt: 426.6806

IMMUNOMODULATING AGENTS

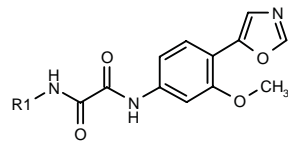
309261

*N*¹-[1,1-Dimethyl-2-(4-nitrophenyl)ethyl]-*N*²-[3-methoxy-4-(5-oxazolyl)phenyl]oxamide



C22 H22 N4 O6; Mol wt: 438.4378

ACTION – An inhibitor of IMP dehydrogenase (IMPDH; IC₅₀ = 0.010 μM) with potential as an immunosuppressant, as well as for the treatment of cancer, microbial and parasitic infections, inflammation and vascular hyperproliferation. Other exemplified oxamides include the following:



Compound	R1	Formula
309262	3-(PhCONHCH2)-Ph	C ₂₆ H ₂₂ N ₄ O ₅
309263	C(Me)2CH2Ph	C ₂₂ H ₂₃ N ₃ O ₄
309264	3-(PhOCONHCH2)-Ph	C ₂₆ H ₂₂ N ₄ O ₆

SOURCE – Roche.

REFERENCES

1. Broadhurst, M.J. et al. (F. Hoffmann-La Roche AG) *Oxamides as IMPDH inhibitors*. EP 1127883, JP 2001261663.

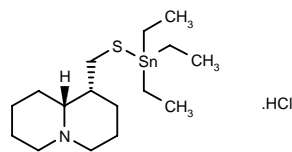
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

IST-FS-29

311056

(1*R*,9*aR*)-1-(Triethylstannylsulfanylmethyl)perhydroquinolizine hydrochloride



C16 H33 N S Sn . HCl; Mol wt: 426.6806

ACTION – Antineoplastic agent, an organotin compound with *in vitro* cytotoxic activity against a panel of human cancer cells including Jurkat and MOLT-4 leukemia cells (IC₅₀ = 0.77 and 2.99 μM, respectively), small cell lung carcinoma NCI-N592 and non-small cell lung carcinoma A549 (2.23 and 2.94 μM, respectively), colon adenocarcinoma HCT 116 and HCT-8 (IC₅₀ = 3.24 and 4.69 μM, respectively), breast adenocarcinoma MDA-MB-231 and MCF-7 (IC₅₀ = 6.05 and 7.85 μM, respectively), and ovarian carcinoma SW 626, IGROV1 and OVCAR-3 cells (IC₅₀ = 0.9, 0.7 and 0.5 μM). *In vivo* in mice bearing P388 leukemia, compound at doses of 3.5-14 mg/kg i.p. induced a dose-dependent and statistically significant reduction in tumor growth of 25-46%. When administered to mice bearing B16 melanoma or 3LL Lewis lung carcinoma as repeated oral doses of 21 mg/kg, significant inhibition (70 and 90%, respectively) of tumor volume was found. No severe toxicity was seen at up to 14 mg/kg i.p., whereas the dose of 21 mg/kg i.p. produced important histological alterations and severe body weight loss.

SOURCES – Università degli Studi di Genova, Genova (IT); Istituto Nazionale Ricerca sul Cancro, Genova (IT).

REFERENCES

1. Barbieri, F. et al. *Antiproliferative activity and interactions with cell-cycle related proteins of the organotin compound triethyltin(IV)lupinylsulfide hydrochloride*. Chem-Biol Interact 2001, 134(1): 27.

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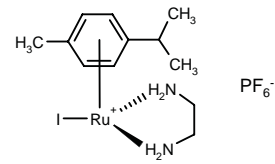
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RM-121

296240

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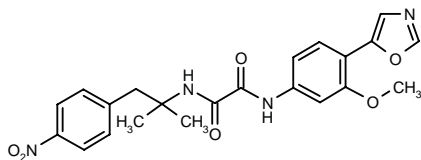
C12 H22 F6 I N2 P Ru; Mol wt: 567.2518

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IMMUNOMODULATING AGENTS

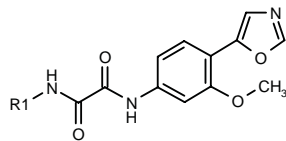
309261

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SOURCE – Roche.

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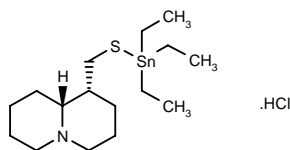
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

IST-FS-29

311056

(1*R*,9*aR*)-1-(Triethylstannylsulfanylmethyl)perhydro-quinolizine hydrochloride



C16 H33 N S Sn . HCl; Mol wt: 426.6806

ACTION – Antineoplastic agent, an organotin compound with *in vitro* cytotoxic activity against a panel of human cancer cells including Jurkat and MOLT-4 leukemia cells (IC₅₀ = 0.77 and 2.99 μM, respectively), small cell lung carcinoma NCI-N592 and non-small cell lung carcinoma A549 (2.23 and 2.94 μM, respectively), colon adenocarcinoma HCT 116 and HCT-8 (IC₅₀ = 3.24 and 4.69 μM, respectively), breast adenocarcinoma MDA-MB-231 and MCF-7 (IC₅₀ = 6.05 and 7.85 μM, respectively), and ovarian carcinoma SW 626, IGROV1 and OVCAR-3 cells (IC₅₀ = 0.9, 0.7 and 0.5 μM). *In vivo* in mice bearing P388 leukemia, compound at doses of 3.5-14 mg/kg i.p. induced a dose-dependent and statistically significant reduction in tumor growth of 25-46%. When administered to mice bearing B16 melanoma or 3LL Lewis lung carcinoma as repeated oral doses of 21 mg/kg, significant inhibition (70 and 90%, respectively) of tumor volume was found. No severe toxicity was seen at up to 14 mg/kg i.p., whereas the dose of 21 mg/kg i.p. produced important histological alterations and severe body weight loss.

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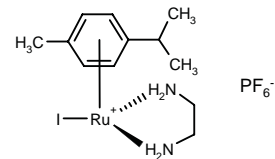
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RM-121

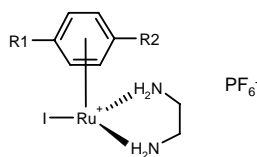
296240

(1,2-Ethanediamine-κ*N*,κ*N*')iodo[(1,2,3,4,5,6-η)-1-isopropyl-4-methylbenzene]ruthenium(II) hexafluorophosphate



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Compound	R1	R2	Formula
RM-116 [296235]	Me	i-Pr	C ₁₂ H ₂₂ ClF ₆ N ₂ PRu
RM-175 [296238]	H	Ph	C ₁₄ H ₁₈ ClF ₆ N ₂ PRu

SOURCES – Cancer Research UK; University of Edinburgh, Edinburgh (GB).

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3. Morris, R.E. et al. *Inhibition of cancer cell growth by ruthenium(II) arene complexes*. J Med Chem 2001, 44(22): 3616.

ANTIMETABOLITES

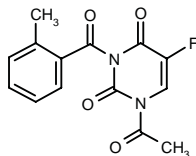
ATOFLUDING

110413

1-Acetyl-3-(*o*-toluyl)-5-fluorouracil

1-Acetyl-5-fluoro-3-(2-methylbenzoyl)pyrimidine-2,4(1*H*,3*H*)-dione

A-OT



C14 H11 F N2 O4; Mol wt: 290.2489

ACTION – Double prodrug of 5-fluorouracil (5-FU) with broad-spectrum antineoplastic activity in murine tumor models. Compound was well tolerated in animals and did not affect cardiovascular and behavioral parameters in dogs and mice. Pharmacokinetic experiments showed that it was rapidly metabolized to 3-*O*-toluyl-5-fluorouridine (TFU) and 5-FU in mice and rabbits, whereas in humans it was rapidly converted to TFU and more slowly to 5-FU. In a multicenter, randomized phase II study, it was found to produce complete remissions of gastric, colon and esophageal tumors in 25% of patients. Currently in phase III studies in China.

SOURCES – Taiho; Xian Pharmaceutical Factory.

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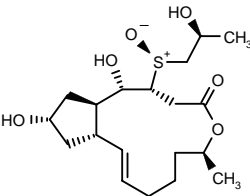
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ANTIBIOTICS AND ALKALOIDS

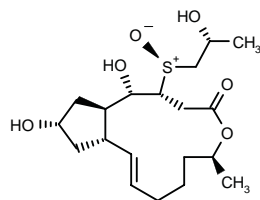
310548

(1*S*,2*R*,6*S*,11*aS*,13*S*,14*aR*)-1,13-Dihydroxy-2-[2(*S*)-hydroxypropyl-(*S*_s)-sulfinyl]-6-methyl-2,3,4,6,7,8,9,11*a*,12,13,14,14*a*-dodecahydro-1*H*-cyclopenta[*f*]oxa-cyclotridecin-4-one



C19 H32 O6 S; Mol wt: 388.5218

ACTION – Antineoplastic antibiotic, a brefeldin A sulfide prodrug with increased water solubility and comparable *in vitro* toxicity against a panel of human cancer cell lines including colon cancer HCT 116, CNS cancer SF-539, melanoma UACC-62, ovarian carcinoma OVCAR-3, renal cancer SN12C, prostate cancer DU 145 and breast cancer MDA-MB-435 cells. Another related compound is:



310549: C19 H32 O6 S

SOURCE – Purdue University, West Lafayette, IN (US).

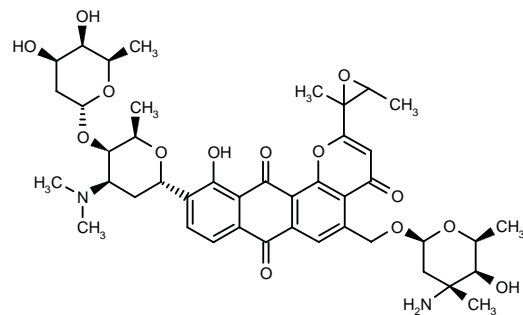
REFERENCES

1. Fox, B.M. et al. *Preparation and evaluation of sulfide derivatives of the antibiotic brefeldin A as potential prodrug candidates with enhanced aqueous solubilities.* J Med Chem 2001, 44(23): 3915.

PLURAFLAVIN A^{1,2}

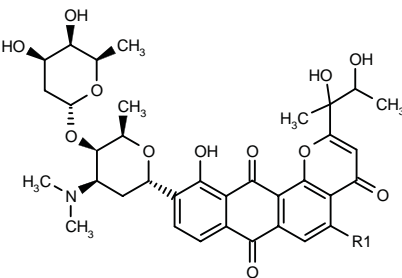
308540

5-(3-Amino-2,3,6-trideoxy-3-methyl-β-L-xylo-hexopyranosyloxymethyl)-2-(2,3-dimethyloxiran-2-yl)-11-hydroxy-10-[2,3,6-trideoxy-4-O-(2,6-dideoxy-α-D-lyxo-hexapyranosyl)-3-(dimethylamino)-α-D-lyxo-hexopyranosyl]-7,12-dihydro-4H-anthra[1,2-b]pyran-4,7,12-trione



C43 H54 N2 O14; Mol wt: 822.8996

ACTION – Antineoplastic antibiotic isolated from the culture of *Saccharothrix* sp. DSM 12931, able to inhibit gluco-6-phosphatase gene transcription with an IC₅₀ < 50 nM and to inhibit the *in vitro* growth of some human cancer cells including prostate PC-3, colon COLO 205, non-small cell lung carcinoma NCI-H460 and leukemia HL-60 cells (IC₅₀ = 10, 0.35, 1 and 0.08 nM, respectively). Other related compounds are:



Compound	R1	Formula
Pluraflavin B [308541] ^{1,2}	3-NH2-3-Me-2,3,6-trideoxy-β-L-xylo-hexopyranosyl-OCH2	C ₄₃ H ₅₆ N ₂ O ₁₅
Pluraflavin E [310161] ²	CO2H	C ₃₆ H ₄₁ NO ₁₄

SOURCE – Aventis Pharma.

REFERENCES

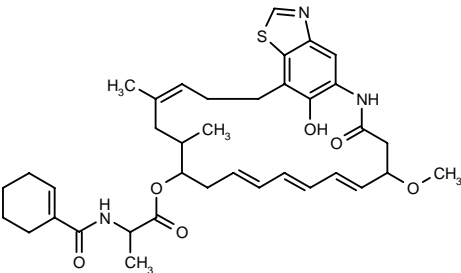
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2. Vértésy, L. et al. *Pluraflavins, potent antitumor antibiotics from Saccharothrix sp. DSM 12931.* J Antibiot 2001, 54(9): 718.

THIAZINOTRIENOMYCIN F

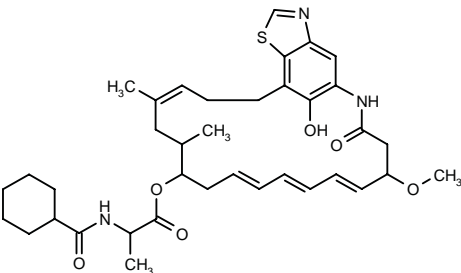
309323

2-(1-Cyclohexen-1-ylcarboxamido)propionic acid 25-hydroxy-9-methoxy-18,20-dimethyl-7-oxo-6,7,8,9,16,17,18,19,22,23-decahydro-24,5-methenothiazolo[4,5-d]-azacyclotricosin-17-yl ester



C37 H47 N3 O6 S; Mol wt: 661.8593

ACTION – Antitumor antibiotic isolated from *Streptomyces* sp. MJ672-m3 (FERM P-14047). *In vitro*, this compound was shown to display activity against human cervical cancer HeLa S3, maxillary cancer KB, gastric cancer SC-6, leukemia HL-60, lung cancer LX-1 and colon cancer COLO 201 cells, with respective IC₅₀ values of 25, 10, 13, 50, 186 and 120 mg/ml. Another compound isolated from the same source is:



Thiazinotrienomycin G [309325]: C37 H49 N3 O6 S

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

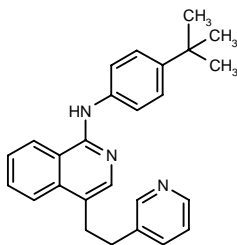
REFERENCES

1. Takeuchi, T. et al. (Microbial Chemistry Research Foundation) *Antitumor antibiotic thiazinotrienomycin F and G, and antibiotic benzo-oxazomycin*. JP 2001199988.

ANGIOGENESIS INHIBITORS

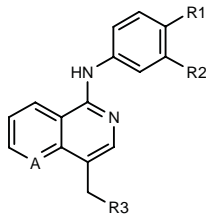
308734

N-(4-*tert*-Butylphenyl)-4-[2-(3-pyridyl)ethyl]isoquinolin-1-amine



C26 H27 N3; Mol wt: 381.5203

ACTION – Antiangiogenic agent, a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (IC₅₀ = 0.025 μM) proven to inhibit VEGF-induced KDR autophosphorylation in transfected CHO cells with an ED₅₀ of 0.010 μM. Potentially useful for the treatment of proliferative diseases including cancer. Other exemplified pyridine derivatives are:



Compound	R1	R2	R3	A	Formula
308735	i-Pr	Me	3-Pyr-CH2	CH	C ₂₆ H ₂₇ N ₃
308736	Et	Br	3-Pyr-CH2	CH	C ₂₄ H ₂₂ BrN ₃
308737	t-Bu	H	6-MeO-3-Pyr	CH	C ₂₆ H ₂₇ N ₃ O
308738	t-Bu	H	6-OH-3-Pyr	CH	C ₂₅ H ₂₆ N ₃ O
308739	Et	Br	6-OH-3-Pyr	CH	C ₂₃ H ₂₀ BrN ₃ O
308740	t-Bu	H	6-MeO-3-Pyr	N	C ₂₅ H ₂₆ N ₄ O
308741	t-Bu	H	6-OH-3-Pyr	N	C ₂₄ H ₂₄ N ₄ O

SOURCE – Novartis.

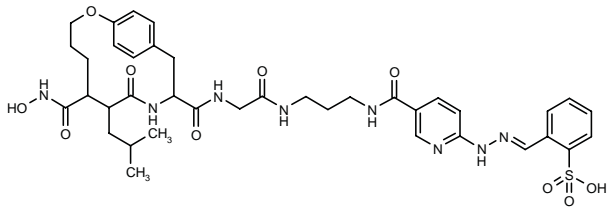
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309139

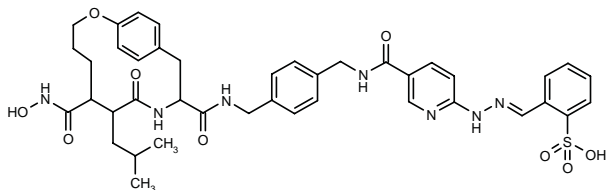
2-[*N*-[5-[*N*-[3-[2-[6-(*N*-Hydroxycarbamoyl)-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-trien-10-ylcarboxamido]acetamido]propyl]carbamoyl]pyridin-2-yl]hydrazonomethyl]benzenesulfonic acid

7-Isobutyl-8-oxo-10-[*N*-[*N*-[3-[6-[2-(2-sulfobenzylidene)-hydrazino]pyridin-3-ylcarboxamido]propyl]carbamoyl-methyl]carbamoyl]-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6-carbohydroxamic acid



C38 H48 N8 O10 S; Mol wt: 808.9092

ACTION – Matrix metalloproteinase (MMP) inhibitor suitable for the preparation of complexes with diagnostic imageable moieties or cytotoxic radioisotopes, particularly ^{99m}Tc, for the diagnosis and treatment of pathologies associated with extracellular matrix degradation such as cancer, diabetic retinopathy and macular degeneration. Another specifically claimed compound is:



309140: C41 H47 N7 O9 S

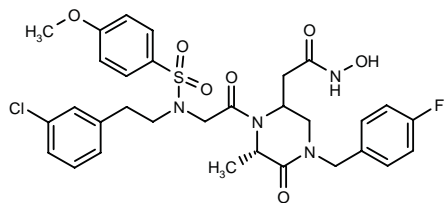
SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

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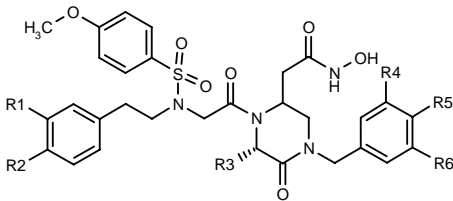
309393

2-[1-[2-[*N*-[2-(3-Chlorophenyl)ethyl]-*N*-(4-methoxyphenyl-sulfonyl)amino]acetyl]-4-(4-fluorobenzyl)-6(*S*)-methyl-5-oxopiperazin-2-yl]acetohydroxamic acid isomer A



C31 H34 Cl F N4 O7 S; Mol wt: 661.1476

ACTION – Matrix metalloproteinase (MMP) inhibitor (IC_{50} = 0.05 μ M against MMP-9 [gelatinase B]), potentially useful for the treatment of cancer, tumor metastasis, arthritis and multiple sclerosis. Other exemplified heterocyclic hydroxamic acids are:



Compound	R1	R2	R3	R4=R6	R5	Formula
309394	Cl	H	Me	H	F	C ₃₁ H ₃₄ ClFN ₄ O ₇ S
309395	Cl	H	H	H	F	C ₃₀ H ₃₂ ClFN ₄ O ₇ S
309396	H	OMe	H	H	F	C ₃₁ H ₃₅ FN ₄ O ₈ S
309397	H	OMe	Me	H	F	C ₃₂ H ₃₇ FN ₄ O ₈ S
309398	Cl	H	H	OMe	H	C ₃₂ H ₃₇ ClN ₄ O ₉ S
309399	H	OMe	H	OMe	H	C ₃₃ H ₄₀ N ₄ O ₁₀ S
309400	Cl	H	Me	OMe	H	C ₃₃ H ₃₉ ClN ₄ O ₉ S
309401	H	OMe	Me	OMe	H	C ₃₄ H ₄₂ N ₄ O ₁₀ S

SOURCE – Advanced SynTech.

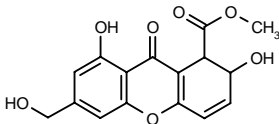
REFERENCES

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ACRL-B4

310158

2,8-Dihydroxy-6-(hydroxymethyl)-9-oxo-2,9-dihydro-1 H-xanthene-1-carboxylic acid methyl ester



C16 H14 O7; Mol wt: 318.2796

ACTION – Antiangiogenic compound isolated from *Aspergillus* sp. Y80118, considered to have potential in the treatment of cancer, arthritis and diabetic retinopathy. *In vitro*, compound was able to inhibit vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cell (HUVEC) proliferation. In the chorio-allantoic membrane (CAM) assay, it inhibited angiogenesis by 90% at 5 μ g/CAM. When administered at 30 mg/kg i.p., it inhibited the growth of lung carcinoma 3LL and melanoma B16-BL6 xenografts transplanted s.c. to mice by 80 and 65%, respectively, while producing no side effects. The oral LD_{50} of the title compound in rats was found to be > 500 mg/kg.

SOURCES – Kolon Industries; Korea Research Institute of Bioscience and Biotechnology, Taedok Science Town (KR).

REFERENCES

1. Lee, J.J. et al. (Korea Research Institute of Bioscience and Biotechnology;Kolon Industries, Inc.) *Novel 7,8-dihydro-xanthenone-8-carboxylic acid deriv. and novel microbe producing the same*. WO 0166783.

MAb HUIV-26

308047

Murine monoclonal antibody against the cryptic site within type IV collagen play an essential role in angiogenesis

ACTION – Murine monoclonal antibody directed against the cryptic site of proteolyzed subendothelial type IV collagen, able to disrupt integrin-dependent endothelial cell interactions, as well as to strongly inhibit angiogenesis in several animal models and the growth of several tumor types of distinct histological origin including hamster melanoma CS1, human fibrosarcoma HT-1080 and human melanoma M21 cells. Moreover, in a mouse model of ischemia-induced retinal neovascularization, compound (1-20 mg/kg/day s.c. for 5 days) inhibited retinal neovascularization in a dose-dependent manner. Potentially useful for the treatment of neoplastic diseases, as well as diabetic retinopathy.

SOURCES – Cell Matrix; University of Southern California, Los Angeles, CA (US).

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2. Brooks, P.C. *Proteolytic exposure of a cryptic site within collagen-IV regulates angiogenesis and tumor growth in vivo*. FASEB J 2000, 14(4): Abst 15.2.

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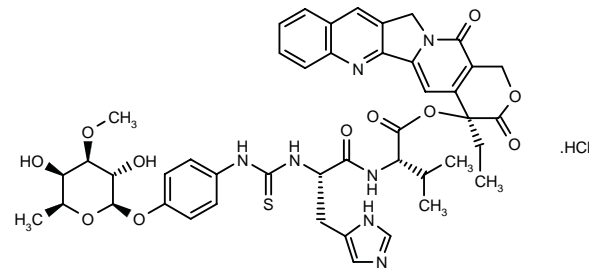
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DNA-INTERCALATING DRUGS

BAY-38-3441*

271380

N-[4-(6-Deoxy-3-*O*-methyl- β -L-galactopyranosyloxy)-phenylaminothiocarbonyl]-L-histidyl-L-valine 4(*S*)-ethyl-3,14-dioxo-3,4,12,14-tetrahydro-1 *H*-pyrano[3',4':6,7]-indolizino[1,2-*b*]quinolin-4-yl ester hydrochloride



C45 H49 N7 O11 S . HCl; Mol wt: 932.4470

ACTION – Antineoplastic agent, a camptothecin glyco-conjugate designed to stabilize the lactone form of camptothecin in blood, thereby increasing its availability for active uptake into tumor cells. Compound exhibited good *in vitro* cytotoxic activity against human colon cancer HT-29 and SW480 cells (IC_{50} = 60 and 100 nM, respectively). *In vivo* in human tumor xenograft models in mice, compound showed potent activity against non-small cell lung cancer LXFL529, colon cancer HT-29 and CXF 280, breast cancer MX-1 and prostate cancer DU 145. When compound was administered daily for 30 days in the breast cancer MX-1 tumor model, curative effects were seen at 2, 4 and 6 mg/kg p.o. Compared with topotecan, compound had markedly reduced toxicity to hematopoietic cells and primary hepatocytes *in vitro*. Preliminary results of a phase I study in cancer patients showed that compound as a single 30-min i.v. infusion every 3 weeks at doses of 20, 40, 67, 100, 140 and 210 mg/m² was generally well tolerated at all dose levels tested and the maximum tolerated dose (MTD) was not reached.

SOURCE – Bayer.

REFERENCES

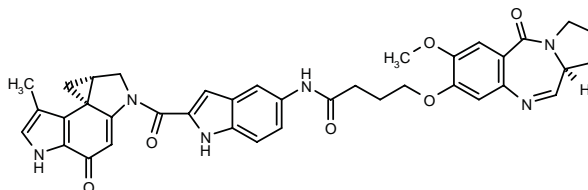
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- Fiebig, H.H. et al. *Anticancer activity of novel camptothecin glycoconjugates in human tumor xenografts models*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 667.
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- Lerchen, H.-G. et al. *Design and optimization of 20-O-linked camptothecin glycoconjugates*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 666.
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*Identified compound **271380** Drug Data Rep 1999, 021(03): 0265.

UTA-6026

310700

4-[(11a*S*)-7-Methoxy-5-oxo-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-8-yloxy]-*N*-[2-[(7*bR*,8a*S*)-7-methyl-4-oxo-1,2,4,5,8,8a-hexahydro-cyclopropa[*c*]pyrrolo[3,2-*e*]indol-2-ylcarbonyl]-1*H*-indol-5-yl]butyramide



C38 H36 N6 O6; Mol wt: 672.7384

ACTION – DNA interstrand adenine–guanine crosslinking agent with strong cytotoxic activity in several tumor cell lines including breast cancer MCF-7, colon cancer SW480 and non-small cell lung cancer A549 cells (IC_{50} = 0.28, 0.047 and 5.1 nM, respectively).

SOURCES – Arizona Cancer Center, Tucson, AZ (US); University of Arizona, Tucson, AZ (US); University of Texas System, Austin, TX (US).

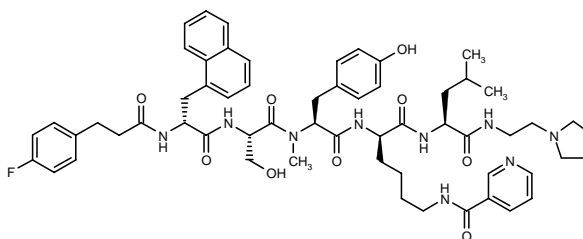
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HORMONAL AGENTS

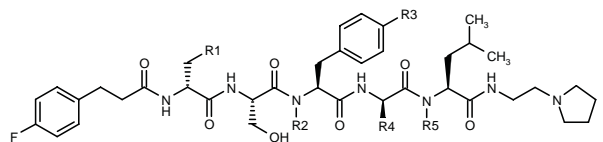
310032

N-[3-(4-Fluorophenyl)propionyl]-3-(1-naphthyl)-*D*-alanyl-*L*-seryl-*N*-methyl-*L*-tyrosyl-*N*⁶-(pyridin-3-ylcarbonyl)-*D*-lysyl-*L*-leucine [2-(1-pyrrolidinyl)ethyl]amide

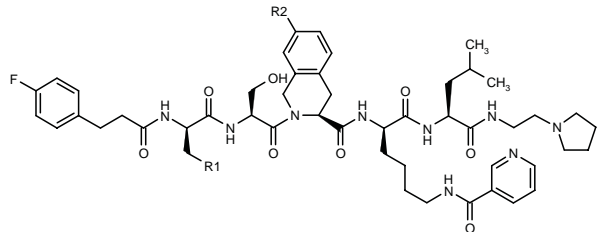


C59 H74 F N9 O9; Mol wt: 1072.2860

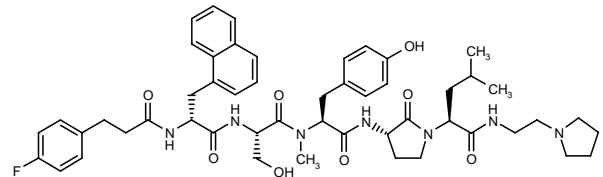
ACTION – Pentapeptide luteinizing hormone-releasing hormone (LHRH) antagonist (pA_2 = 9.91), considered to have potential for the treatment of disorders related to the suppression of sex steroid hormones, particularly delayed puberty, benign prostatic hyperplasia, breast, ovarian and prostate cancer, cryptorchidism, female hirsutism, gastric motility disorders, dysmenorrhea and endometriosis. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
310033	1-Naph	Me	OH	H	H	C ₄₉ H ₆₂ FN ₇ O ₈
310034	1-Naph	H	OH	3-Pyr-CONH(CH ₂) ₄	H	C ₅₈ H ₇₂ FN ₉ O ₉
310035	1-Naph	Me	OH	H	Me	C ₅₀ H ₆₄ FN ₇ O ₈
310036	4-Ph-Ph	Me	H	3-Pyr-CONH(CH ₂) ₄	H	C ₆₁ H ₇₆ FN ₉ O ₈



Compound	R1	R2	Formula
310037	4-Ph-Ph	OH	C ₆₁ H ₇₄ FN ₉ O ₉
310039	1-Naph	H	C ₅₉ H ₇₂ FN ₉ O ₈



310040: C51 H64 F N7 O8

SOURCE – Abbott.

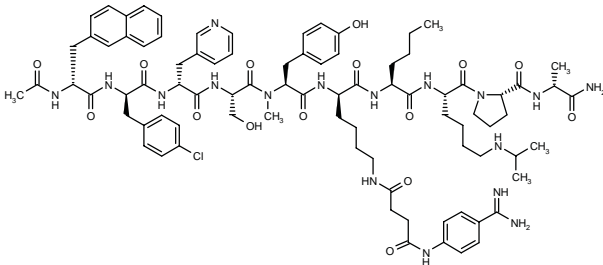
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D-68987

310014

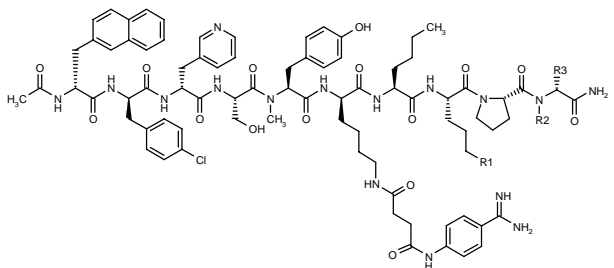
N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-*N*⁶-[3-[*N*-(4-amidinophenyl)carbamoyl]propionyl]-D-lysyl-L-norleucyl-*N*⁶-isopropyl-L-lysyl-L-prolyl-D-alaninamide



C85 H112 Cl N17 O15; Mol wt: 1647.3770

ACTION – Luteinizing hormone-releasing hormone (LHRH) antagonist reported to exhibit increased enzymatic stability and improved water solubility, potentially useful for the treatment of hormone-dependent tumors, particularly prostate cancer and breast cancer, as well as for the treatment of hormone-mediated nonmalignant

diseases such as endometriosis or benign prostatic hyperplasia. Activity was evaluated *in vitro* in a functional assay using cells expressing the human LHRH receptor and a luciferase reporter gene (IC₅₀ = 700 pM vs. 198 pM for cetrorelix). Other exemplified compounds from this series of peptides containing *N*-methylated amino acid building blocks include the following:



Compound	R1	R2	R3	Formula
D-68968 [310018]	NHC(=NH)NH ₂	Me	H	C ₈₂ H ₁₀₆ ClN ₁₉ O ₁₅
D-68969[310021]	NHC(=NH)NH ₂	H	Me	C ₈₂ H ₁₀₆ ClN ₁₉ O ₁₅
D-68971[310022]	i-PrNHCH ₂	Me	H	C ₈₅ H ₁₁₂ ClN ₁₇ O ₁₅

SOURCE – Zentaris.

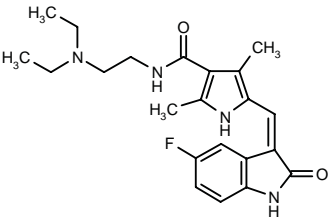
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

309144

N-[2-(Diethylamino)ethyl]-5-(5-fluoro-2-oxo-2,3-dihydro-1*H*-indol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxamide



C22 H27 F N4 O2; Mol wt: 398.4793

ACTION – An inhibitor of protein kinases, particularly receptor tyrosine kinases, nonreceptor protein tyrosine kinases and serine/threonine protein kinases, with potential for the treatment and prevention of diseases mediated by abnormal protein kinase activity such as cancer, diabetes, hepatic cirrhosis, cardiovascular disorders such as atherosclerosis, angiogenesis, autoimmune disorders and renal disorders. *In vitro*, it inhibited GST-Flk-1, FGFR1, PDGF, EGF, Her2 kinase, CDK2 and PYK2 with respective IC₅₀ values of 0.13, 4.29, 0.001, > 100, 50.19, 17.19 and 0.28 μM. In addition, it was shown to inhibit VEGF (vascular endothelial growth factor)-dependent and PDGF (platelet-derived growth factor)-dependent phosphorylation in NIH/3T3 cells expressing Flk-1 or human PDGFR, respectively, with IC₅₀ values of about 0.03 μM. It was further shown to inhibit VEGF- and FGF (fibroblast growth factor)-induced

proliferation of HUVEC (human umbilical vein endothelial cells) with respective IC₅₀ values of 0.004 and 0.7 μM. *In vivo*, it was proven to be effective against human epidermoid carcinoma A-431, human colon carcinoma COLO 205, human non-small cell lung carcinoma NCI-H460 and human glioma SF763T xenografts implanted s.c. in athymic mice when given at 80 mg/kg/day p.o.; in addition, it was effective in the B16F1 mouse melanoma lung colonization model in athymic mice, reducing the burden of B16F1 cells in the lung by 50% when given at 80 mg/kg/day p.o. x 24 days after tumor cell inoculation.

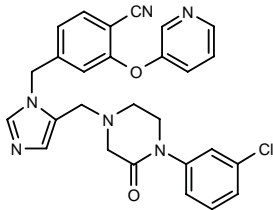
SOURCE – Sugen (Pharmacia).

REFERENCES

1. Tang, P.C. et al. (Sugen, Inc.) *Pyrrole substd. 2-indolinone protein kinase inhibitors*. WO 0160814.

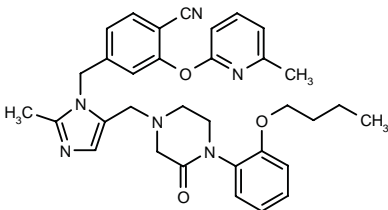
309164

4-[5-[4-(3-Chlorophenyl)-3-oxopiperazin-1-ylmethyl]-1*H*-imidazol-1-ylmethyl]-2-(pyridin-3-yloxy)benzonitrile



C27 H23 Cl N6 O2; Mol wt: 498.9717

ACTION – An inhibitor of protein farnesyltransferase and protein geranylgeranyltransferase type I, potentially useful in the treatment of cancer. Another specifically claimed piperazinone-containing compound is:



309165: C33 H36 N6 O3

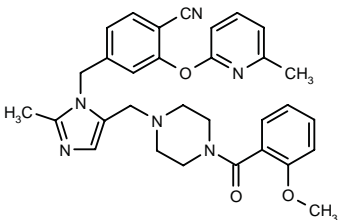
SOURCE – Merck & Co.

REFERENCES

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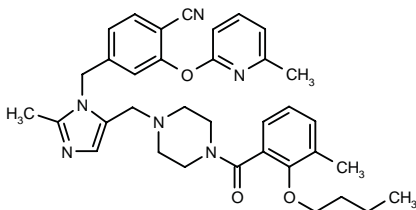
309166

4-[5-[4-(2-Methoxybenzoyl)piperazin-1-ylmethyl]-2-methyl-1*H*-imidazol-1-ylmethyl]-2-(6-methylpyridin-2-yloxy)benzonitrile



C31 H32 N6 O3; Mol wt: 536.6328

ACTION – An inhibitor of protein farnesyltransferase and protein geranylgeranyltransferase type I, potentially useful in the treatment of cancer. Another specifically claimed piperazinone-containing compound is:



309167: C35 H40 N6 O3

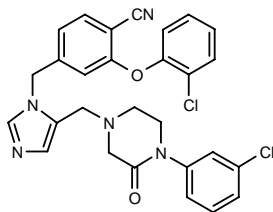
SOURCE – Merck & Co.

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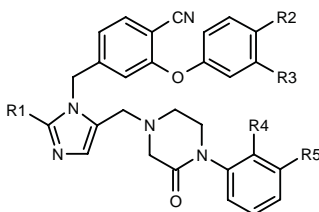
309168

2-(2-Chlorophenoxy)-4-[5-[4-(3-chlorophenyl)-3-oxopiperazin-1-ylmethyl]-1*H*-imidazol-1-ylmethyl]benzonitrile



C28 H23 Cl2 N5 O2; Mol wt: 532.4287

ACTION – An inhibitor of protein farnesyltransferase and protein geranylgeranyltransferase type I, potentially useful in the treatment of cancer. Other specifically claimed piperazinone-containing compounds are:



Compound	R1	R2	R3	R4	R5	Formula
309169	H	H	Cl	H	Cl	C ₂₈ H ₂₃ Cl ₂ N ₅ O ₂
309170	H	Cl	H	H	Cl	C ₂₈ H ₂₃ Cl ₂ N ₅ O ₂
309171	H	Ph	H	H	Cl	C ₃₄ H ₂₈ ClN ₅ O ₂
309172	H	OCH2Ph	H	H	Cl	C ₃₅ H ₃₀ ClN ₅ O ₃
309173	Me	H	OCH2CH2OH	OBu	H	C ₃₅ H ₃₉ N ₅ O ₅

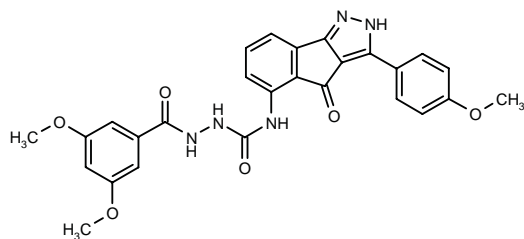
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C.J. and Bergman, J.M. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 0160815.

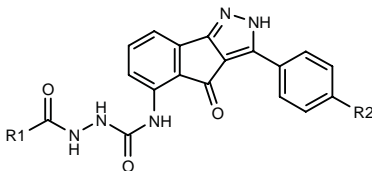
309345

1-(3,5-Dimethoxybenzoyl)-4-[3-(4-methoxyphenyl)-4-oxo-2,4-dihydroindeno[1,2-c]pyrazol-5-yl]semicarbazide



C27 H23 N5 O6; Mol wt: 513.5077

ACTION – An inhibitor of cyclin-dependent kinases (CDKs) that is expected to be useful for the treatment of cancer, as well as other apoptosis-mediated conditions including viral infections, autoimmune diseases and neurodegenerative disorders. Other specifically claimed indeno[1,2-c]pyrazol-4-ones include the following:



Compound	R1	R2	Formula
309346	4-OH-Ph	OMe	C ₂₅ H ₁₉ N ₅ O ₅
309347	4-N(Me)2-Ph	OMe	C ₂₇ H ₂₄ N ₆ O ₄
309348	NH2	OMe	C ₁₉ H ₁₆ N ₆ O ₄
309349	2-Naph	OMe	C ₂₉ H ₂₁ N ₅ O ₄
309350	3-NO2-Ph	OMe	C ₂₅ H ₁₈ N ₆ O ₆
309351	3,4-(OH)2-Ph	OMe	C ₂₅ H ₁₉ N ₅ O ₆
309352	3,5-(MeO)2-Ph	1-Piz	C ₃₀ H ₂₉ N ₇ O ₅

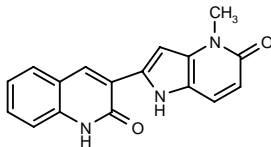
SOURCE – DuPont Pharmaceuticals (Bristol-Myers Squibb).

REFERENCES

1. Nugiel, D.A. et al. (DuPont Pharmaceuticals Co.) *Acylsemicarbazides and their uses*. US 6291504.

309520

3-(4-Methyl-5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-2-yl)quinolin-2(1H)-one



C17 H13 N3 O2; Mol wt: 291.3087

ACTION – An inhibitor of receptor-type and non-receptor-type tyrosine kinases considered to have potential in the treatment and prevention of cancer, as well as other diseases including retinal vascularization, diabetic retinopathy, age-related macular degeneration, inflammatory diseases (particularly arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions), and bone diseases (particularly osteosarcoma, osteoarthritis and rickets). The use of this compound for preventing tissue damage following a cerebral ischemic event is also reported.

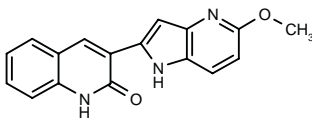
SOURCE – Merck & Co.

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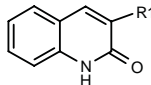
309521

3-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-2-yl)quinolin-2(1H)-one



C17 H13 N3 O2; Mol wt: 291.3087

ACTION – An inhibitor of receptor-type and non-receptor-type tyrosine kinases, considered to have potential in the treatment and prevention of cancer, as well as other diseases including retinal vascularization, diabetic retinopathy, age-related macular degeneration, inflammatory diseases (particularly arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions), and bone diseases (particularly osteosarcoma, osteoarthritis and rickets). The use of this compound for preventing tissue damage following a cerebral ischemic event is also reported. Other specifically claimed heterocyclic compounds are:



Compound	R1	Formula
309522	pyrrolo[2,3-c]pyridin-2-yl	C ₁₆ H ₁₁ N ₃ O
309523	pyrrolo[3,2-c]pyridin-2-yl	C ₁₆ H ₁₁ N ₃ O
309524	pyrrolo[3,2-b]pyridin-2-yl	C ₁₆ H ₁₁ N ₃ O
309525	5-MeO-pyrrolo[2,3-c]pyridin-2-yl	C ₁₇ H ₁₃ N ₃ O ₂
309526	5-oxo-4,5-dihydro-pyrrolo[3,2-b]pyridin-2-yl	C ₁₆ H ₁₁ N ₃ O ₂
309527	5-oxo-5,6-dihydro-pyrrolo[2,3-c]pyridin-2-yl	C ₁₆ H ₁₁ N ₃ O ₂
309528	4-oxo-4,5-dihydro-pyrrolo[3,2-c]pyridin-2-yl	C ₁₆ H ₁₁ N ₃ O ₂

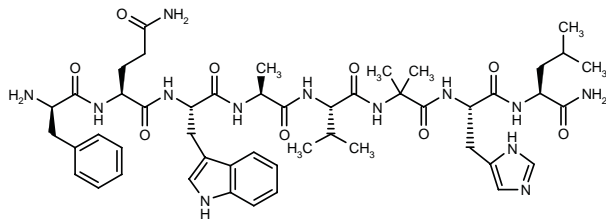
SOURCE – Merck & Co.

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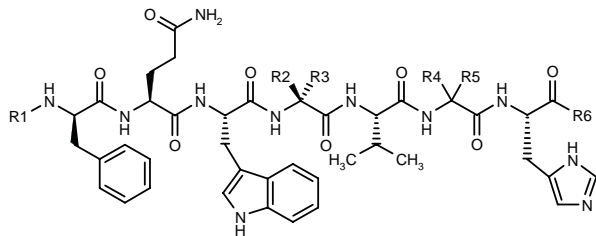
309585

D-Phenylalanyl-L-glutaminy-L-tryptophyl-L-alanyl-L-valyl-2-aminoisobutyryl-L-histidyl-L-leucinamide

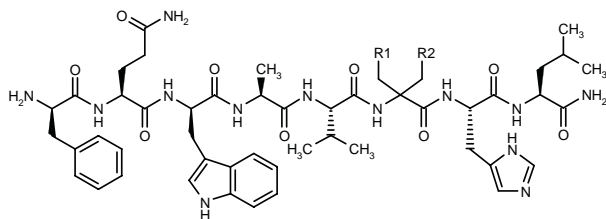


C49 H69 N13 O9; Mol wt: 984.1661

ACTION – Peptide analogue of bombesin that antagonizes bombesin and bombesin-like peptides and is thus expected to be useful as an anticancer agent. *In vitro*, the compound demonstrated activity against a panel of human tumor cell lines. Other exemplified peptides are:



Compound	R1	R2	R3	R4	R5	R6	Formula
309586	H	Me	Me	H	H	-L-Leu-NH2	C ₄₈ H ₆₇ N ₁₃ O ₉
309589	H	Me	Me	H	H	-L-Ile-NH2	C ₄₈ H ₆₇ N ₁₃ O ₉
309590	H	Me	H	Me	Me	-L-Ile-NH2	C ₄₉ H ₆₉ N ₁₃ O ₉
309593	H	Et	Et	H	H	-L-Leu-NH2	C ₅₀ H ₇₁ N ₁₃ O ₉
309594	H	Me	H	-(CH2)4-	H	-L-Leu-NH2	C ₅₁ H ₇₁ N ₁₃ O ₉
309595	COPr	Me	H	Me	Me	-L-Leu-NH2	C ₅₃ H ₇₅ N ₁₃ O ₁₀
309596	COC7H15	Me	H	Me	Me	-L-Leu-NH2	C ₅₇ H ₈₃ N ₁₃ O ₁₀



Compound	R1=R2	Formula
309587	H	C ₄₉ H ₆₉ N ₁₃ O ₉
309591	Et	C ₅₃ H ₇₇ N ₁₃ O ₉

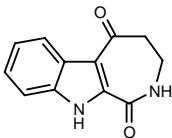
SOURCE – Dabur Research Foundation.

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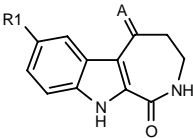
309729

1,2,3,4,5,10-Hexahydroazepino[3,4-*b*]indole-1,5-dione



C12 H10 N2 O2; Mol wt: 214.2230

ACTION – Membrane-associated tyrosine and threonine kinase (myt1 kinase) inhibitor, potentially useful for the treatment of cancer, as well as psoriasis, rheumatoid arthritis, diabetic retinopathy and hemangiomas. Other specifically claimed azepino[3,4-*b*]indole derivatives are:



Compound	R1	A	Formula
309730	Cl	O	C ₁₂ H ₉ ClN ₂ O ₂
309734	H	2-Pyr-NHN=	C ₁₇ H ₁₅ N ₅ O
309735	H	=NNHCONH2	C ₁₃ H ₁₃ N ₅ O ₂
309736	3-furyl	O	C ₁₆ H ₁₂ N ₂ O ₃
309737	3-Pyr	O	C ₁₇ H ₁₃ N ₂ O ₂
309738	3-Pyr-CH2NHCO	=NNHCONH2	C ₂₀ H ₁₉ N ₇ O ₃
309739	2-thienyl-CH2NHCO	O	C ₁₈ H ₁₅ N ₃ O ₃ S
309740	3-Pyr-CH2NHCO	O	C ₁₉ H ₁₆ N ₄ O ₃
309742	4-Pyr-CH2NHCO	O	C ₁₉ H ₁₆ N ₄ O ₃

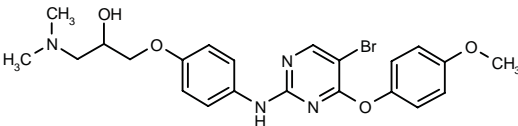
SOURCE – GlaxoSmithKline.

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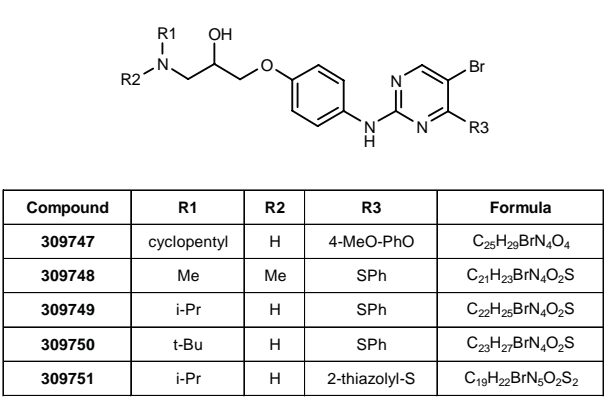
309745

1-[4-[5-Bromo-4-(4-methoxyphenoxy)pyrimidin-2-ylamino]phenoxy]-3-(dimethylamino)propan-2-ol



C22 H25 Br N4 O4; Mol wt: 489.3675

ACTION – An inhibitor of cyclin-dependent serine/threonine kinases (CDKs) with selectivity for CDK2, CDK4 and CDK6 and which also inhibits focal adhesion kinase (FAK). Potentially useful for the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation. Other specifically claimed compounds from this series of substituted pyrimidine derivatives are:



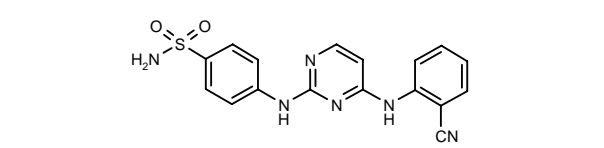
SOURCE – AstraZeneca.

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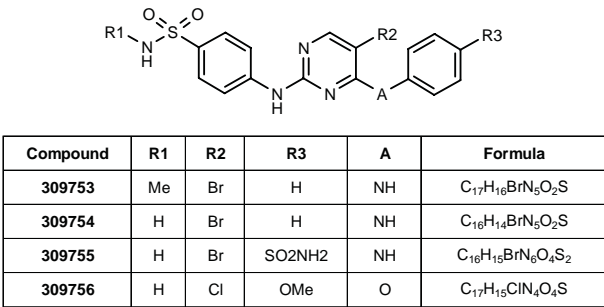
309752

4-[4-(2-Cyanophenylamino)pyrimidin-2-ylamino]benzene-sulfonamide



C17 H14 N6 O2 S; Mol wt: 366.4036

ACTION – An inhibitor of cyclin-dependent serine/threonine kinases (CDKs) with selectivity for CDK2, CDK4 and CDK6 and which also inhibits focal adhesion kinase (FAK). Potentially useful for the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation. Other specifically claimed compounds from this series of substituted pyrimidine derivatives are:



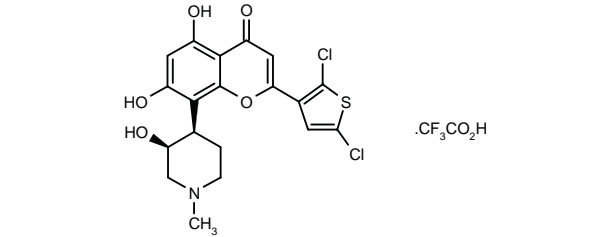
SOURCE – AstraZeneca.

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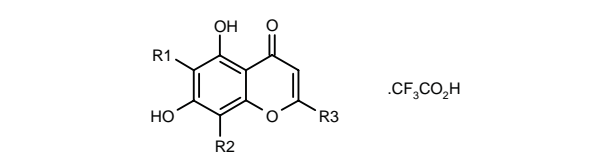
309919

2-(2,5-Dichlorothien-3-yl)-5,7-dihydroxy-8-[3(S)-hydroxy-1-methylpiperidin-4(R)-yl]-4H-1-benzopyran-4-one trifluoroacetate



C19 H17 Cl2 N O5 S . C2 H F3 O2; Mol wt: 556.3392

ACTION – Cyclin-dependent kinase inhibitor, potentially useful for the treatment of cancer, psoriasis and parasitosis. By virtue of its neuronal antiapoptotic activity, this compound may also be useful in the treatment of neurodegenerative diseases, particularly Alzheimer's disease. Other specifically claimed flavone derivatives are:



Compound	R1	R2	R3	Formula
309921	H	3(S)-OH-1-Me-4(R)-Pip	5-Me-3-isoxazolyl	C ₁₉ H ₂₀ N ₂ O ₆ .C ₂ H ₃ F ₃ O ₂
309923	H	3(S)-OH-1-Me-4(R)-Pip	2-Cl-4-F-Ph	C ₂₁ H ₁₉ ClFNO ₅ .C ₂ H ₃ F ₃ O ₂
309926	H	3(S)-OH-1-Me-4(R)-Pip	1-Ph-5-CF3-4-pyrazolyl	C ₂₅ H ₂₂ F ₃ N ₃ O ₅ .C ₂ H ₃ F ₃ O ₂
309927	3(S)-OH-1-Me-4(R)-Pip	H	3-(PhO)-Ph	C ₂₇ H ₂₅ NO ₆ .C ₂ H ₃ F ₃ O ₂

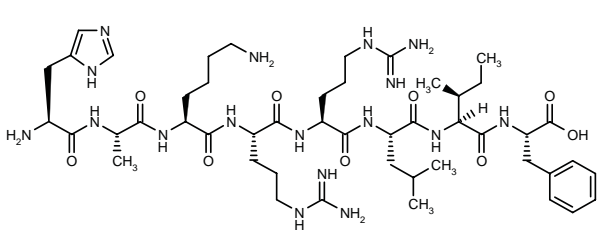
SOURCE – Aventis Pharma.

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310304

L-Histidyl-L-alanyl-L-lysyl-L-arginyl-L-arginyl-L-leucyl-L-isoleucyl-L-phenylalanine



C48 H81 N17 O9; Mol wt: 1040.2780

ACTION – Cyclin-dependent kinase inhibitor, a peptide derived from the C-terminal cyclin-binding domain of the tumor suppressor protein p21 (WAF1), proven to inhibit the activity of cyclin A/CDK2, cyclin E/CDK2 and cyclin D1/CDK4 with respective IC₅₀ values of 21 nM, 0.35 μM and 6 μM, respectively.

SOURCE – Cyclacel.

REFERENCES

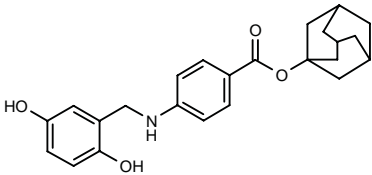
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ADAPHOSTIN*

280448

4-(2,5-Dihydroxybenzylamino)benzoic acid 1-adamantyl ester

NSC-680410



C24 H27 N O4; Mol wt: 393.4803

ACTION – Antileukemic agent, an inhibitor of Bcr/Abl tyrosine kinase proven to inhibit chronic myelogenous leukemia K-562 cell colony formation in soft agar after 24-h exposure ($IC_{50} = 7.3 \mu M$) and to decrease Bcr/Abl autophosphorylation and Bcr/Abl polypeptide levels within 2 h, with consequent cleavage of the caspase substrate poly(ADP-ribose) polymerase (PARP, NAD^+ ADP-ribosyl-transferase) and accumulation of apoptotic cells within 12 h. Compound exhibited significant antileukemic activity in 9 human leukemia clones including wild-type CEM and Jurkat cells and cytarabine-resistant lines, with IC_{50} values ranging from 17 nM to 216 nM.

SOURCES – Mayo Clinic, Rochester, MN (US); National Cancer Institute, Bethesda, MD (US).

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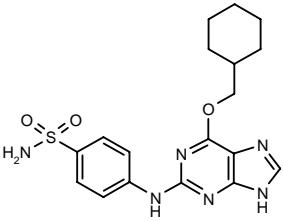
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*Identified compound **280448** Drug Data Rep 1999, 021(11): 1023.

NU-6102

301917

4-[6-(Cyclohexylmethoxy)-9H-purin-2-ylamino]benzene-sulfonamide



C18 H22 N6 O3 S; Mol wt: 402.4768

ACTION – Potent inhibitor of the cyclin-dependent kinases CDK1 and CDK2 ($IC_{50} = 9.5$ and 5.4 nM, respectively) found to be more potent than olomoucine or NU-2058 in inhibiting the growth of human colon carcinoma HCT 116 cells. Unlike the latter compounds, NU-6102 inhibits cell growth in a p53-independent manner and produced significant G₂ arrest and complete loss of cells in the S phase. Potentially useful as an antineoplastic agent.

SOURCES – AstraZeneca; University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

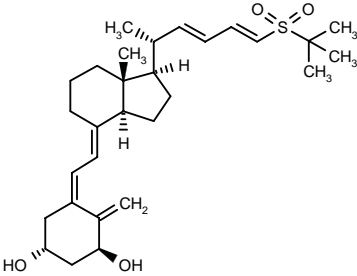
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OTHER ONCOLYTIC DRUGS

308670

(+)-(22E,24E)-25-(tert-Butylsulfonyl)-1 α -hydroxy-22,23,24,25-tetradehydro-26,27-dinorvitamin D₃



C29 H44 O4 S; Mol wt: 488.7286

ACTION – Sulfone analogue of seocalcitol with comparable *in vitro* antiproliferative activity against murine keratinocytes and malignant melanoma cells, as well as against human breast cancer MCF-7 cells. In MCF-7 cells, when compound was added together with doxorubicin, the antiproliferative activity was enhanced by at least 3-fold. Moreover, compound exhibited *in vitro* transcriptional activity in rat osteosarcoma ROS 17/2.8 cells (EC_{50} = 20 nM), bound poorly to the vitamin D receptor and showed no calcemic activity in rats when given at a dose of 10 mcg/kg/day p.o. Potentially useful as an anticancer agent, as well as for enhancing the action of other antineoplastic agents.

SOURCES – Johns Hopkins University, Baltimore, MD (US); M.D. Anderson Cancer Center, Houston, TX (US); University of Notre Dame, Notre Dame, IN (US); Virginia Commonwealth University, Richmond, VA (US).

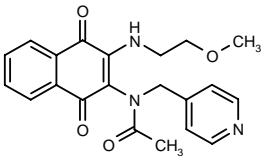
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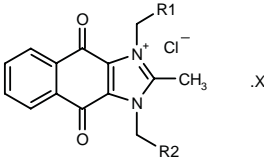
309080

N-[3-(2-Methoxyethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-(pyridin-4-ylmethyl)acetamide

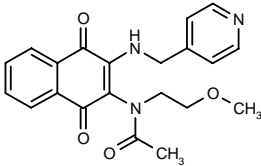


C21 H21 N3 O4; Mol wt: 379.4139

ACTION – Antineoplastic agent with excellent antitumor activity and low toxicity. *In vitro*, it gave IC_{50} values < 1 μ M against cervical cancer HeLaS3 and melanoma A-375 cell lines. *In vivo*, compound showed antitumor activity against melanoma A-375 xenografts implanted s.c. in nude mice when given at 0.3-1 mg/kg/day i.v. for 2 weeks. No deaths were observed following a single i.v. dose of 3 mg/kg to mice. Other exemplified fused imidazolium derivatives are:



Compound	R1	R2	X	Formula
309082	CH2N(Me)2	H	HCl	C ₁₇ H ₂₀ ClN ₃ O ₂ ·HCl
309083	CH2OMe	CH2OMe		C ₁₈ H ₂₁ ClN ₂ O ₄
309084	2-pyrazinyl	CH2OMe		C ₂₀ H ₁₉ ClN ₄ O ₃
309085	3-Pyr	CH2OMe	HCl	C ₂₁ H ₂₀ ClN ₃ O ₃ ·HCl
309086	4-Pyr	CH2OMe	HCl	C ₂₁ H ₂₀ ClN ₃ O ₃ ·HCl



309081: C21 H21 N3 O4

SOURCE – Yamanouchi.

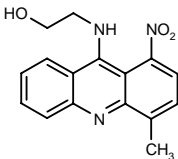
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309146

2-(4-Methyl-1-nitroacridin-9-ylamino)ethanol

9-(2-Hydroxyethylamino)-4-methyl-1-nitroacridine



C16 H15 N3 O3; Mol wt: 297.3125

ACTION – A representative compound from a series of nitroacridine derivatives with antitumor activity. It demonstrated *in vivo* activity in a panel of tests, with an optimal i.p. dose of 4 mg/kg/day against Walker carcinosarcoma 256 cells inoculated i.p. in rats. Compound was able to reduce by 65% the size of Dunning G tumors injected s.c. to rats following i.p. administration at 0.8 mg/kg twice weekly for 3 weeks. Finally, almost complete disappearance of human prostate cancer TSU xenografts implanted s.c. in nude mice was observed after treatment with compound at 0.8 mg/kg twice weekly for 3 weeks.

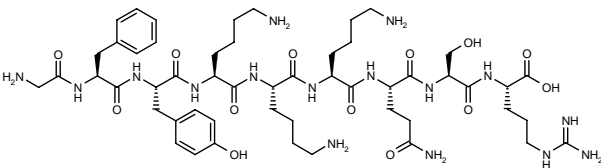
SOURCE – New York Medical College, Valhalla, NY (US).

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309422

Glycyl-L-phenylalanyl-L-tyrosyl-L-lysyl-L-lysyl-L-lysyl-L-glutaminyl-L-seryl-L-arginine



C52 H84 N16 O13; Mol wt: 1141.3350

ACTION – Prostate-specific antigen (PSA) inhibitor, as demonstrated *in vitro* by its ability to suppress the degradation of human recombinant IGF-binding protein-3 (IGFBP-3). Potentially useful for the treatment of prostate cancer and prostatic hyperplasia.

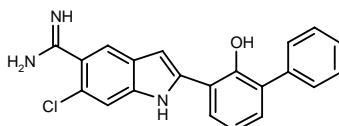
SOURCE – JCR Pharmaceuticals.

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310486

6-Chloro-2-(2-hydroxybiphenyl-3-yl)-1*H*-indole-5-carboxamide



C21 H16 Cl N3 O; Mol wt: 361.8304

ACTION – Potent and selective inhibitor of urokinase-type plasminogen activator (u-PA; $K_i = 9$ nM) with > 10-fold selectivity over serine proteases such as plasmin, trypsin and factor VIIa and > 150-fold selectivity over factor Xa, plasma kallikrein, thrombin and tissue-type plasminogen activator (tPA). Compound showed a favorable pharmacokinetic profile, suitable for twice-daily dosing. Potentially useful for the treatment of tumors and metastases.

SOURCE – Axys Pharmaceuticals.

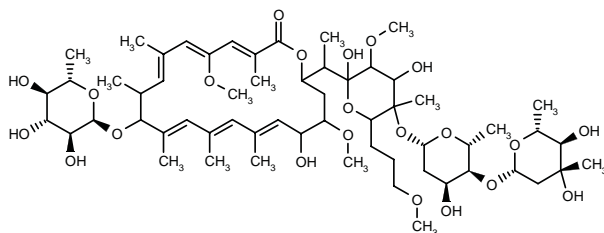
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AMMOCIDIN

309087

10-(6-Deoxy- α -L-glucopyranosyloxy)-20-[1-[5-[4-*O*-(2,6-dideoxy-3-*C*-methyl- β -D-glucopyranosyl)- β -D-allopyranosyloxy]-2,4-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydropyran-2-yl]ethyl]-17-hydroxy-5,18-dimethoxy-3,7,9,11,13,15-hexamethyloxacyclicosa-3,5,7,11,13,15-hexaen-2-one



C59 H96 O22; Mol wt: 1157.3850

ACTION – Selective apoptosis inducer isolated from the culture broth of *Saccharothrix* sp. AJ9571, able to induce apoptotic cell death in Ras-dependent Ba/F3-V12 cells ($IC_{50} = 66$ ng/ml). Compound significantly reduced phosphorylation of mitogen-activated protein kinase (MAPK) and S6 kinase, which mediate the antiapoptotic function of Ras in these cells.

SOURCE – Ajinomoto.

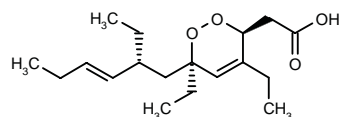
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HATERUMADIOXIN A

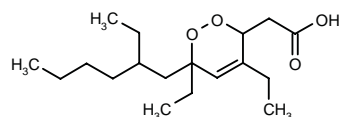
305750

2-[4,6(*R*)-Diethyl-6-[2(*R*)-ethyl-3-hexenyl]-3,6-dihydro-1,2-dioxin-3(*S*)-yl]acetic acid



C18 H30 O4; Mol wt: 310.4310

ACTION – Antineoplastic agent, a cytotoxic endoperoxide extracted from the Okinawan sponge *Plakortis lita* found to be active *in vitro* against a panel of human cancer cell lines, particularly melanoma LOX IMVI cells. Another related compound is:



Haterumadioxin B [305751]: C18 H32 O4

SOURCE – Sagami.

REFERENCES

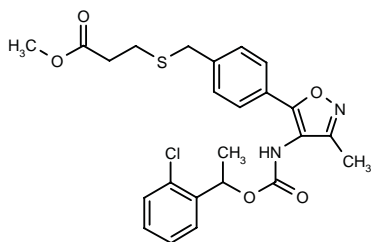
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ID-3016511

309079

3-[4-[4-[1-(2-Chlorophenyl)ethoxycarbonylamino]-3-methylisoxazol-5-yl]benzylsulfanyl]propionic acid methyl ester

N-[5-[4-(3-Methoxy-3-oxopropylsulfanylmethyl)phenyl]-3-methylisoxazol-4-yl]carbamic acid 1-(2-chlorophenyl)ethyl ester



C₂₄ H₂₅ Cl N₂ O₅ S; Mol wt: 488.9895

ACTION – Agent for the treatment of restenosis, arteriosclerosis, inflammation, nephropathy, tumor growth and metastasis, and cerebral or peripheral nerve disorders, a lysophosphatidic acid (LPA) receptor antagonist. *In vitro*, it inhibited LPA-induced increases in intracellular Ca²⁺ in human edg2-expressing HepG2 cells (IC₅₀ = 1-3 μM) and it was shown to inhibit LPA-induced [³H]-thymidine uptake in these cells (IC₅₀ = 0.01-0.03 μM). In addition, it concentration-dependently (0.3-10 μM) inhibited LPA-induced increases in bromovinyldeoxyuridine uptake in human brain tumor U-87 MG and human ovarian cancer SK-OV-3 cells. When tested *in vivo* in a rat model of lactic acid-induced peripheral circulatory disorder, it was shown to significantly reduce paw lesions when given at 60 mg/kg/day p.o. b.i.d. x 13 days. A representative compound from a series of isoxazole and thiazole derivatives.

SOURCE – Kirin Brewery.

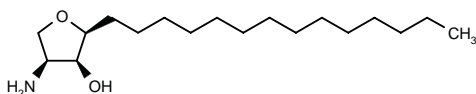
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IK-8-73-4

308987

4(*S*)-Amino-2(*S*)-tetradecyltetrahydrofuran-3(*S*)-ol



C₁₈ H₃₇ N O₂; Mol wt: 299.4953

ACTION – Antineoplastic spissulosine analogue isolated from the marine sponge *Pachastrissa* sp., displaying an IC₅₀ of 0.01 μg/ml against murine leukemia P388, human lung cancer A549, human colon cancer HT-29 and human melanoma MEL-28 cell lines.

SOURCE – PharmaMar.

REFERENCES

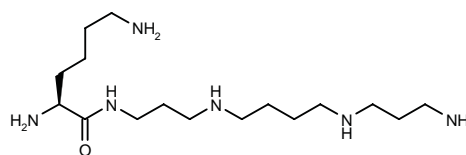
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ORI-1202

283489

L-Lysine *N*-[3-[4-(3-aminopropylamino)butylamino]propyl]-amide

Lys-Spm



C₁₆ H₃₈ N₆ O; Mol wt: 330.5172

ACTION – Spermine-lysine conjugate able to strongly inhibit the uptake of polyamines into human breast cancer MDA-MB-231 cells (K_i = 320, 240 and 840 nM for uptake of spermidine, putrescine and spermine, respectively) and to inhibit the growth of several human cancer cell lines *in vitro* including breast, prostate, bladder carcinoma and melanoma cells in the presence of α-(difluoromethyl)-ornithine (DFMO; EC₅₀ = 1.5-4.8 μM). Preliminary *in vivo* experiments in nude mice bearing MDA-MB-231 xenografts showed that compound at 45 mg/kg i.p. t.i.d. 5 days/week for 2 weeks given with DFMO produced 50% tumor growth inhibition, which was significantly greater than that produced by either compound alone. No gross acute toxicity or weight loss was seen.

SOURCE – Oridigm.

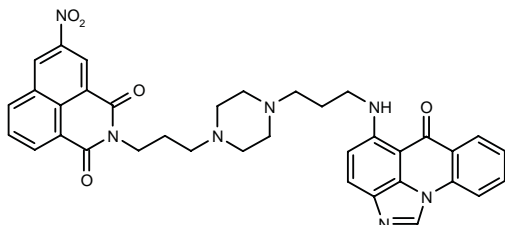
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6. Weeks, R.S. et al. *Novel lysine-spermine conjugate alters in vitro and in vivo tumor cell growth through inhibition of polyamine transport*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 189.
7. Weeks, R.S. et al. *Novel lysine-spermine conjugate inhibits polyamine transport and inhibits cell growth when given with DFMO*. Exp Cell Res 2000, 261(1): 293.
8. Weeks, R.S. et al. *Polyamine transport and synthesis inhibition can inhibit in vitro and in vivo prostate cell growth*. Eur Urol 2000, 37(Suppl. 2): Abst 31.
9. *Current Research*. Oridigm Web Site 2000, July 14

WMC-79

310082

5-Nitro-2-[3-[4-[3-(6-oxo-6H-imidazo[4,5,1-de]acridin-5-ylamino)propyl]piperazin-1-yl]propyl]benzo[de]isoquinoline-1,3(2H)-dione



C36 H33 N7 O5; Mol wt: 643.7007

ACTION – Antineoplastic agent with potent and selective activity against human colon cancer HCT 116 cells (IC_{50} = 0.4 pM) and human pancreatic cancer 10.05 cells (IC_{50} = 2 nM), being more potent in HCT 116 cells carrying wild-type *p53* suppressor gene. Compound produced cell death via apoptosis in the colon, pancreatic and human leukemia HL-60 cells, and induced G_1 and G_2/M arrest. *In vivo* studies in nude mice bearing HCT 116 or human 10.05 tumor xenografts also demonstrated antitumor activity following i.v. administration.

SOURCE – National Cancer Institute, Bethesda, MD (US).

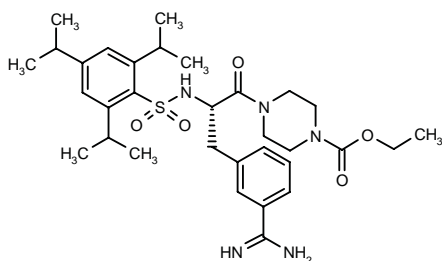
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WX-UK1*

288028

4-[3-(3-Amidinophenyl)-2(*S*)-(2,4,6-triisopropylphenyl)sulfonamido]propionyl]piperazine-1-carboxylic acid ethyl ester



C32 H47 N5 O5 S; Mol wt: 613.8193

ACTION – Broad-spectrum, low-molecular-weight inhibitor of cancer-related serine proteases including urokinase-type plasminogen activator (uPA), plasmin and thrombin (K_i = 0.41, 0.39 and 0.49 μ M, respectively), proven to inhibit tumor growth and metastasis in the hormone-independent mammary carcinoma BN-472 model in rats with a minimum effective dose range of 0.15-0.3 mg/kg s.c. Compound showed rapid biliary elimination but was retained in several tissues with a half-life of up to

several days. Moreover, it has low organotoxic potential and was not genotoxic in standard assays.

SOURCES – Pentapharm; Wilex.

REFERENCES

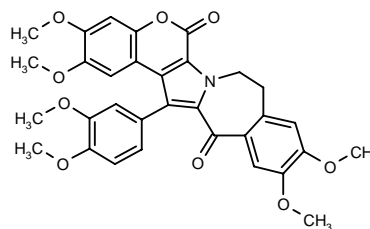
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8. WX-UK1: The first urokinase inhibitor to enter clinical trials. DailyDrugNews.com (Daily Essentials) 2001, Sept 25.

*Identified compound **288028** Drug Data Rep 2000, 022(07): 0649.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

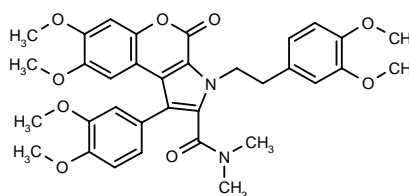
309842

15-(3,4-Dimethoxyphenyl)-2,3,11,12-tetramethoxy-6,8,9,14-tetrahydro-1-benzopyrano[4',3':4,5]pyrrolo-[2,1-b][3]benzazepine-6,14-dione



C32 H29 N O9; Mol wt: 571.5791

ACTION – A ningalin B analogue with the ability to reverse multidrug resistance (MDR) to anticancer drugs while displaying no inherent cytotoxicity. *In vitro*, this compound was shown to sensitize the resistant human colon cancer cell line HCT 116/VM46 to vinblastine and doxorubicin at concentrations in the low micromolar range. Another exemplified ningalin analogue is:



309843: C34 H36 N2 O9

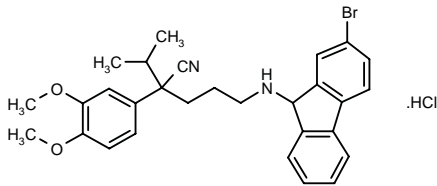
SOURCE – Scripps Research Institute, La Jolla, CA (US).

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310419

5-(2-Bromo-9H-fluoren-9-ylamino)-2-(3,4-dimethoxy-phenyl)-2-isopropylpentanenitrile hydrochloride



C29 H31 Br N2 O2 . HCl; Mol wt: 555.9408

ACTION – Multidrug resistance modulator (MDR) with good MDR-reversing activity in anthracycline-resistant erythroleukemia K-562 cells and high affinity for P-glycoprotein ($K_i = 0.08 \mu\text{M}$). Compound is devoid of cardiovascular side effects.

SOURCES – Università degli Studi di Bologna, Bologna (IT); Università degli Studi di Firenze, Firenze (IT); Université Paris Nord, Villetaneuse (FR).

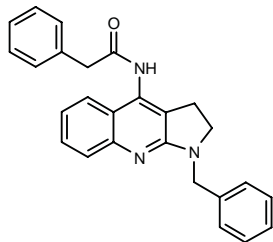
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PGP-4008

310337

N-(1-Benzyl-2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-4-yl)-2-phenylacetamide



C26 H23 N3 O; Mol wt: 393.4877

ACTION – Multidrug resistance modulator shown to selectively inhibit the P-glycoprotein drug transporter in several *in vitro* assays. In mice bearing doxorubicin-resistant leukemia P388/ADR, combined treatment with compound (75 mg/kg i.p.) and doxorubicin (0.5 mg/kg i.p.) increased life span by 125% compared to doxorubicin alone. Compound at the dose of 75 mg/kg i.p. in mice rapidly achieved peak plasma levels (2 mg/ml), which were higher than the concentrations effective *in vitro* (0.8 mg/ml), and showed good penetration of the blood–brain barrier, wide distribution to organs and significant hepatic metabolism.

SOURCE – Pennsylvania State University, Hershey, PA (US).

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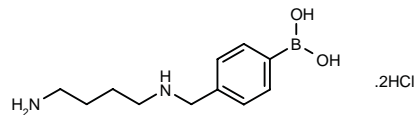
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RADIATION THERAPY

4-BBZ-PUT

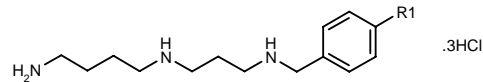
309989

4-(4-Aminobutylaminomethyl)phenylboronic acid dihydrochloride



C11 H19 B N2 O2 . 2HCl; Mol wt: 295.0159

ACTION – Putrescine derivative suitable as a vector of boron for boron neutron capture therapy (BNCT) for the treatment of melanoma. Compound selectively accumulated in CHO cells with polyamine active transport compared to polyamine transport-deficient CHO-MG cells, and did not show significant cytotoxicity in lung carcinoma 3LL cells ($IC_{50} > 1000 \mu\text{M}$). In melanoma B16 cells, compound allowed accumulation of boron up to 5 $\mu\text{g B/g}$ and pretreatment of cells with eflornithine (DFMO) increased accumulation of boron about 4 times, reaching levels of 18 $\mu\text{g B/g}$. Other *N*-benzylpolyamines are:



Compound	R1	Formula
N1-4-Bbz-spd [309990]	B(OH)2	C ₁₄ H ₂₆ BN ₃ O ₂ ·3HCl
N1-4-Fbz-spd [310260]	F	C ₁₄ H ₂₄ FN ₃ ·3HCl

SOURCE – CNRS.

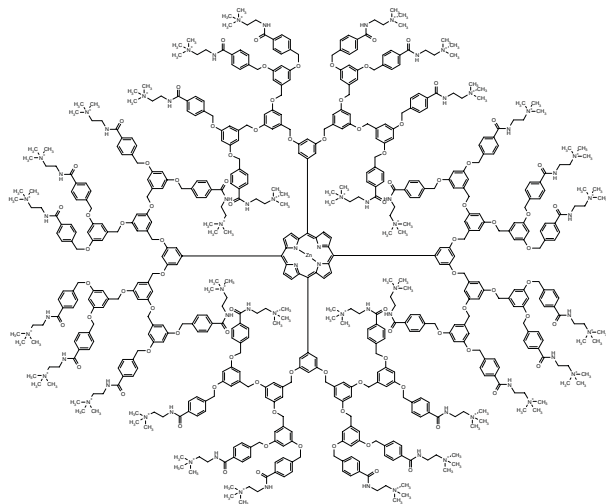
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PHOTODYNAMIC THERAPY

309237

24-Cascade:porphyrin[4-5,10,15,20]:[1,3,5-phenylene]:[5-(2-oxaethyl)-1,3-phenylene]:[5-(2-oxaethyl)-1,3-phenylene]:[4-(2-oxaethyl)-N-[2-(trimethylammonium)-ethyl]benzamide]zinc complex



C628 H780 N68 O88 Zn; Mol wt: 10754.8500

ACTION – A representative compound from a series of ionic porphyrin derivatives for use in the photodynamic therapy of tumors. *In vitro*, compound exhibited cytotoxicity following light irradiation against Lewis lung carcinoma ($EC_{50} = 0.2 \mu\text{M}$ vs. $10 \mu\text{M}$ in the absence of light).

SOURCE – Japan Science and Technology.

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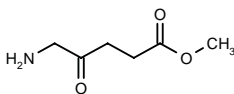
METVIX®

283660

5-Amino-4-oxopentanoic acid methyl ester

5-Aminolevulinic acid methyl ester

P-1202



C6 H11 N O3; Mol wt: 145.1569

ACTION – Photodynamic therapy that combines the local application of a cream (aminolevulinic acid methyl ester) followed by activation of the drug through illumination with a proprietary red light source (CureLight).

INDICATION – Treatment of actinic keratoses and basal cell carcinoma in patients in whom traditional therapies are considered less suitable.

PRESENTATION – Cream.

PROPRIETARY NAME – Metvix (SE).

SOURCE – PhotoCure.

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10. *Phase III results with Metvix PDT for primary BCC reported as positive.* DailyDrugNews.com (Daily Essentials) 2001, Jan 10.

11. *Phase III trial of Metvix PDT indicates superiority to surgery in nodular BCC.* DailyDrugNews.com (Daily Essentials) 2001, April 20.

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15. *PhotoCure reports highlights from 2000 and goals for 2001.* DailyDrugNews.com (Daily Essentials) 2001, Feb 20.

16. *PhotoCure reports preliminary results from phase III trial of Metvix in basal cell carcinoma.* DailyDrugNews.com (Daily Essentials) 2001, Nov 20.

17. *PhotoCure reports update on company progress during the first quarter.* DailyDrugNews.com (Daily Essentials) 2001, May 10.

18. *PhotoCure seeks E.U. approval of Metvix for second indication.* DailyDrugNews.com (Daily Essentials) 2001, Jan 18.

19. *PhotoCure seeks marketing approval for Metvix(R) PDT in New Zealand.* DailyDrugNews.com (Daily Essentials) 2001, April 30.

20. *PhotoCure's Metvix PDT receives European approval.* DailyDrugNews.com (Daily Essentials) 2001, Dec 4.

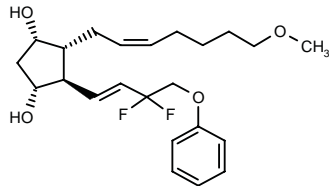
21. *Positive phase III results announced for Metvix PDTas treatment of actinic keratosis.* DailyDrugNews.com (Daily Essentials) 2001, March 7.

22. *Results of phase III Metvix study show superiority to cryotherapy in treatment of AK.* DailyDrugNews.com (Daily Essentials) 2001, Jan 17.

OCULAR MEDICATIONS

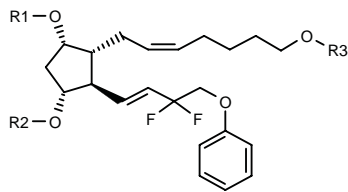
309238

1-Deoxo-15-deoxy-15,15-difluoro-16-phenoxy-17,18,19,20-tetranorprostaglandin F_{2α} methyl ester

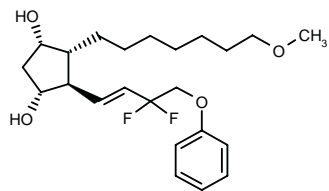


C23 H32 F2 O4; Mol wt: 410.4978

ACTION – Prostaglandin analogue shown to be able to lower intraocular pressure (IOP) when administered to monkeys in the form of eye drops. Potentially useful for the treatment of glaucoma and ocular hypertension. Other exemplified difluoroprostaglandin analogues are:



Compound	R1	R2	R3	Formula
309239	H	Me	t-BuCO	C ₂₈ H ₄₀ F ₂ O ₅
309242	H	H	Ac	C ₂₄ H ₃₂ F ₂ O ₅
309244	Me	H	H	C ₂₃ H ₃₂ F ₂ O ₄
309245	Me	H	Ac	C ₂₅ H ₃₄ F ₂ O ₅
309247	H	H	t-BuCO	C ₂₇ H ₃₈ F ₂ O ₅



309241: C23 H34 F2 O4

SOURCE – Asahi Glass.

REFERENCES

1. Tanaka, T. et al. (Asahi Glass Co., Ltd.) *Novel difluoroprostaglandin deriv.* WO 0155102.

LATANOPROST/TIMOLOL MALEATE

New combination

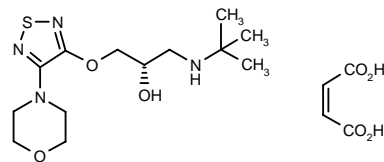
285222

Fixed combination of latanoprost and timolol maleate

Timolol mateale

(S)-1-(1,1-Dimethylethylamino)-3-[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yloxy]-2-propanol maleate

091506

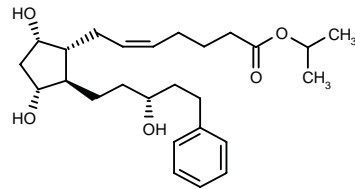


C13 H24 N4 O3 S . C4 H4 O4 ; Mol wt: 432.4952

Latanoprost

(15R)-17-Phenyl-13,14-dihydro-18,19,20-trinorprosta-glandin F_{2α} isopropyl ester

183029



C26 H40 O5 ; Mol wt: 432.6060

ACTION – Combination of the selective FP receptor agonist latanoprost and the nonselective β₁- and β₂-adrenoceptor antagonist timolol.

INDICATION – Reduction of intraocular pressure in patients with open-angle glaucoma and ocular hyper-tension who are insufficiently responsive to topical β-blockers.

PRESENTATION – Solution (eye drops) containing latanoprost 50 µg/ml and timolol maleate 6.8 mg/ml equivalent to 5 mg/ml timolol.

PROPRIETARY NAMES – Xalacom (GB); Xalcom (SE).

SOURCE – Pharmacia.

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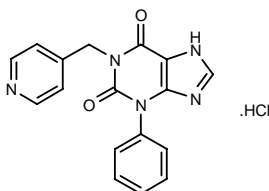
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

308868

3-Phenyl-1-(pyridin-4-ylmethyl)-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride

3-Phenyl-1-(pyridin-4-ylmethyl)-7H-xanthine hydrochloride



C₁₇ H₁₃ N₅ O₂ · HCl; Mol wt: 355.7836

ACTION – A representative compound from series of xanthine derivatives with bone resorption-inhibitory activity. Potentially useful for the prevention and treatment of osteoporosis, as well as hypercalcemia, osteopenia, hyperparathyroidism, Paget's disease and rheumatoid arthritis.

SOURCE – Aventis Pharma.

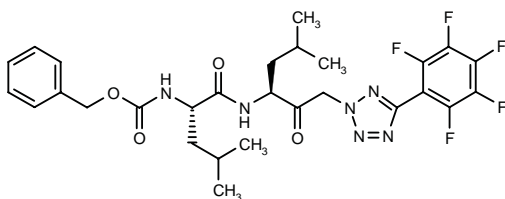
REFERENCES

1. Billen, G.J. et al. (Aventis Pharma SA) *Xanthine derivs., intermediates and use for treating osteoporosis.* FR 2804958, WO 0160824.

309640

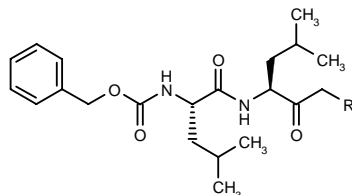
*N*²-(Benzyloxycarbonyl)-*N*¹-[3-methyl-1(*S*)-[2-[5-(pentafluorophenyl)-2*H*-tetrazol-2-yl]acetyl]butyl]-L-leucinamide

2-[*N*-(Benzyloxycarbonyl)-L-leucyl-L-leucylmethyl]-5-(pentafluorophenyl)-2*H*-tetrazole



C₂₈ H₃₁ F₅ N₆ O₄; Mol wt: 610.5809

ACTION – An inhibitor of cysteine proteases such as cathepsins, with a *K_i* value of 0.021 μM against cathepsin K. Potentially useful for the treatment of a broad range of disorders including inflammatory diseases, apoptosis, immune and autoimmune diseases, shock, circulatory disorders, blood coagulation disorders, cancer, AIDS, neurodegenerative diseases, bone resorption diseases and endocrine disorders. Other exemplified nitrogen-containing 5-membered cyclic compounds include the following:



Compound	R1	Formula
309641	3-(4-F-Ph)-5-oxo-4,5-dihydro-1,2,4-oxadiazol-4-yl	C ₂₉ H ₃₅ FN ₄ O ₆
309642	2-oxo-5-(PhCH2CH2)-2,3-dihydro-1,3,4-oxadiazol-3-yl	C ₃₁ H ₄₀ N ₄ O ₆

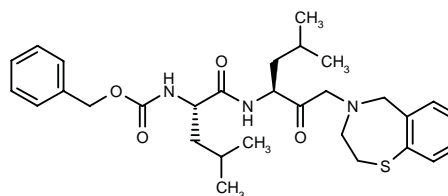
SOURCE – Ono.

REFERENCES

1. Ohmoto, K. and Itagaki, I. (Ono Pharmaceutical Co., Ltd.) *Nitrogen-containing 5-membered cyclic cpds. and drugs containing these cpds. as the active ingredient.* WO 0155123.

309643

*N*²-(Benzyloxycarbonyl)-*N*¹-[3-methyl-1(*S*)-[2-[2,3,4,5-tetrahydro-1,4-benzothiazepin-4-yl]acetyl]butyl]-L-leucinamide



C₃₀ H₄₁ N₃ O₄ S; Mol wt: 539.7369

ACTION – An inhibitor of cysteine proteases such as cathepsins, with a *K_i* value of 0.081 μM against cathepsin K. Potentially useful for the treatment of a broad range of disorders including inflammatory diseases, apoptosis, immune and autoimmune diseases, shock, circulatory disorders, blood coagulation disorders, cancer, AIDS, neurodegenerative diseases, infectious diseases, bone resorption diseases and endocrine disorders. Other exemplified benzene-fused heterocyclic compounds include the following:

7. *Monsanto and Pharmacia & Upjohn outline additional merger details, late-stage products.* DailyDrugNews.com (Daily Essentials) 2000, Feb 7.

8. *Pharmacia & Upjohn seeks approval for combination glaucoma therapy.* DailyDrugNews.com (Daily Essentials) 2000, Jan 11.

9. *Q2 2001 at Pharmacia marked by three E.U. approvals, making way for upcoming market launches.* DailyDrugNews.com (Daily Essentials) 2001, Aug 2.

10. *Update on Pharmacia's ocular medications.* DailyDrugNews.com (Daily Essentials) 2000, Oct 24.

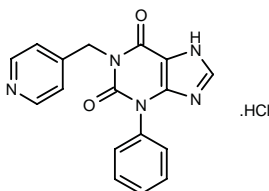
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

308868

3-Phenyl-1-(pyridin-4-ylmethyl)-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride

3-Phenyl-1-(pyridin-4-ylmethyl)-7H-xanthine hydrochloride



C₁₇ H₁₃ N₅ O₂ · HCl; Mol wt: 355.7836

ACTION – A representative compound from series of xanthine derivatives with bone resorption-inhibitory activity. Potentially useful for the prevention and treatment of osteoporosis, as well as hypercalcemia, osteopenia, hyperparathyroidism, Paget's disease and rheumatoid arthritis.

SOURCE – Aventis Pharma.

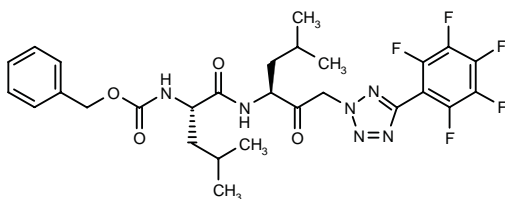
REFERENCES

1. Billen, G.J. et al. (Aventis Pharma SA) *Xanthine derivs., intermediates and use for treating osteoporosis.* FR 2804958, WO 0160824.

309640

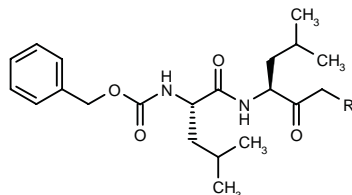
*N*²-(Benzyloxycarbonyl)-*N*¹-[3-methyl-1(*S*)-[2-[5-(pentafluorophenyl)-2*H*-tetrazol-2-yl]acetyl]butyl]-L-leucinamide

2-[*N*-(Benzyloxycarbonyl)-L-leucyl-L-leucylmethyl]-5-(pentafluorophenyl)-2*H*-tetrazole



C₂₈ H₃₁ F₅ N₆ O₄; Mol wt: 610.5809

ACTION – An inhibitor of cysteine proteases such as cathepsins, with a *K_i* value of 0.021 μM against cathepsin K. Potentially useful for the treatment of a broad range of disorders including inflammatory diseases, apoptosis, immune and autoimmune diseases, shock, circulatory disorders, blood coagulation disorders, cancer, AIDS, neurodegenerative diseases, bone resorption diseases and endocrine disorders. Other exemplified nitrogen-containing 5-membered cyclic compounds include the following:



Compound	R1	Formula
309641	3-(4-F-Ph)-5-oxo-4,5-dihydro-1,2,4-oxadiazol-4-yl	C ₂₉ H ₃₅ FN ₄ O ₆
309642	2-oxo-5-(PhCH2CH2)-2,3-dihydro-1,3,4-oxadiazol-3-yl	C ₃₁ H ₄₀ N ₄ O ₆

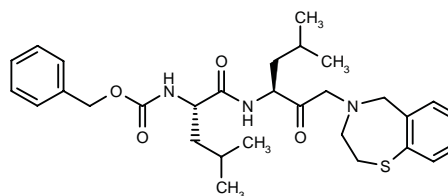
SOURCE – Ono.

REFERENCES

1. Ohmoto, K. and Itagaki, I. (Ono Pharmaceutical Co., Ltd.) *Nitrogen-containing 5-membered cyclic cpds. and drugs containing these cpds. as the active ingredient.* WO 0155123.

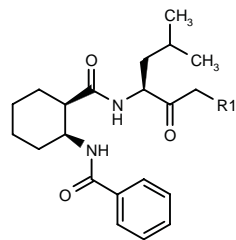
309643

*N*²-(Benzyloxycarbonyl)-*N*¹-[3-methyl-1(*S*)-[2-[2,3,4,5-tetrahydro-1,4-benzothiazepin-4-yl]acetyl]butyl]-L-leucinamide

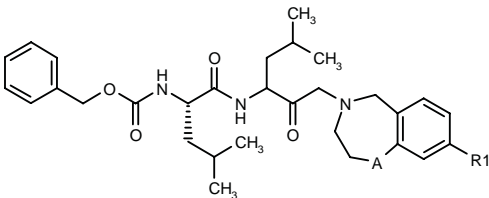


C₃₀ H₄₁ N₃ O₄ S; Mol wt: 539.7369

ACTION – An inhibitor of cysteine proteases such as cathepsins, with a *K_i* value of 0.081 μM against cathepsin K. Potentially useful for the treatment of a broad range of disorders including inflammatory diseases, apoptosis, immune and autoimmune diseases, shock, circulatory disorders, blood coagulation disorders, cancer, AIDS, neurodegenerative diseases, infectious diseases, bone resorption diseases and endocrine disorders. Other exemplified benzene-fused heterocyclic compounds include the following:



Compound	R1	Formula
309644	2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl	C ₃₁ H ₄₁ N ₃ O ₃
309646	2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl	C ₃₁ H ₄₁ N ₃ O ₃



Compound	R1	A	Isomer	Formula
309645	H	CH2	S	C ₃₁ H ₄₃ N ₃ O ₄
309647	OH	CH2		C ₃₁ H ₄₃ N ₃ O ₅
309648	H	N(i-Pr)	S	C ₃₃ H ₄₈ N ₄ O ₄

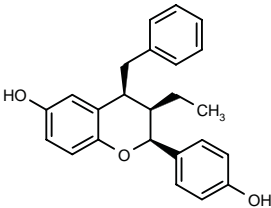
SOURCE – Ono.

REFERENCES

1. Ohmoto, K. and Itagaki, I. (Ono Pharmaceutical Co., Ltd.) *Benzene-fused heterocycle derivs. and drugs containing the same as the active ingredient.* WO 0155118.

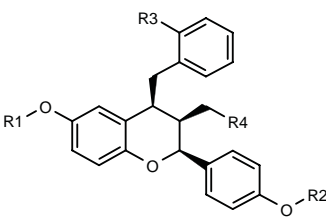
309769

4(S)-Benzyl-3(R)-ethyl-2(S)-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-6-ol



C24 H24 O3; Mol wt: 360.4506

ACTION – Agent with affinity for estrogen receptors (ER) proven active in a luciferase transactivation assay in CHO cells, with over 30-fold selectivity for the ERβ receptor subtype. Potentially useful for the treatment of osteoporosis, cardiovascular disorders, benign prostatic hypertrophy, depression and Alzheimer’s disease, among other estrogen receptor-related disorders. Other exemplified chroman derivatives include the following:



Compound	R1=R2	R3	R4	Formula
309770	H	F	Me	C ₂₄ H ₂₃ FO ₃
309771	H	F	H	C ₂₃ H ₂₁ FO ₃
309772	COPr	H	Me	C ₃₂ H ₃₆ O ₅

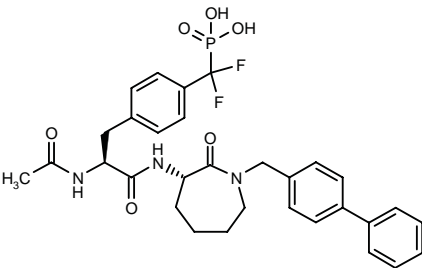
SOURCE – Akzo Nobel.

REFERENCES

1. Veeneman, G.H. and Teerhuis, N.M. (Akzo Nobel N.V.) *Chroman derivs. as estrogenic cpds.* WO 0164665.

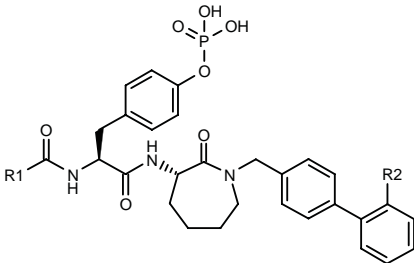
310023

N²-Acetyl-N¹-[1-(biphenyl-4-ylmethyl)-2-oxoperhydroazepin-3(S)-yl]-4-(1,1-difluoro-1-phosphonomethyl)-L-phenylalaninamide



C31 H34 F2 N3 O6 P; Mol wt: 613.5946

ACTION – Src kinase SH2 receptor antagonist (IC₅₀ = 0.005 μM) that inhibits bone resorption and is thus expected to be useful for the treatment of osteoporosis. Further applications include autoimmune, proliferative, inflammatory or cardiovascular diseases. Other exemplified caprolactam derivatives include the following:



Compound	R1	R2	Formula
310024	t-BuO	H	C ₃₃ H ₄₀ N ₃ O ₈ P
310025	Me	CN	C ₃₁ H ₃₃ N ₄ O ₇ P

SOURCE – Ariad Pharmaceuticals.

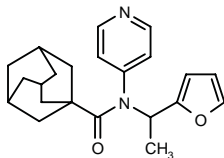
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1. Deprez, P. et al. (Ariad Pharmaceuticals Inc.) *Caprolactam derivs. and uses thereof.* WO 0168655.

TREATMENT OF LIPOPROTEIN DISORDERS

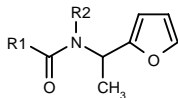
308988

N-[1-(2-Furyl)ethyl]-*N*-(4-pyridyl)adamantane-1-carboxamide



C22 H26 N2 O2; Mol wt: 350.4594

ACTION – Liver X receptor LXR α agonist expected to be useful for the treatment of conditions associated with the metabolism of cholesterol and bile acids, particularly atherosclerosis and hypercholesterolemia. Other exemplified compounds are:



Compound	R1	R2	Formula
308989	1-adamantyl	2-Pyr	C ₂₂ H ₂₆ N ₂ O ₂
308990	1-adamantyl	3-Pyr	C ₂₂ H ₂₆ N ₂ O ₂
308991	1-adamantyl	Ph	C ₂₃ H ₂₇ NO ₂
308992	1-Me-cyclohexyl	2-Pyr-CH(Me)	C ₂₁ H ₂₈ N ₂ O ₂

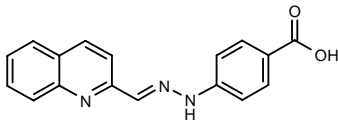
SOURCE – Tularik.

REFERENCES

1. Li, L. et al. (Tularik Inc.) *LXR modulators*. WO 0160818.

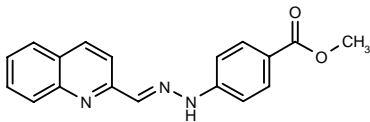
309840

4-[2-(Quinolin-2-ylmethylene)hydrazino]benzoic acid



C17 H13 N3 O2; Mol wt: 291.3087

ACTION – Agent for the treatment of lipoprotein disorders that acts by directly or indirectly upregulating the synthesis of low-density lipoprotein (LDL) receptors. By virtue of its activity, this compound may be useful for the treatment of hypercholesterolemia, hyperlipidemia and related disorders. Another specifically claimed hydrazone analogue is:



309841: C18 H15 N3 O2

SOURCES – Sumitomo Pharmaceuticals; Tularik.

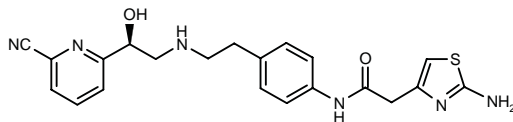
REFERENCES

1. Medina, J.C. and Hasegawa, H. (Tularik, Inc.; Sumitomo Pharmaceuticals Co., Ltd.) *Hydrazones and analogs as cholesterol lowering agents*. WO 0164646.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

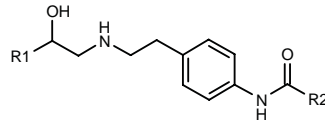
309222

2-(2-Aminothiazol-4-yl)-*N*-[4-[2-[2(*S*)-(6-cyanopyridin-2-yl)-2-hydroxyethylamino]ethyl]phenyl]acetamide



C21 H22 N6 O2 S; Mol wt: 422.5108

ACTION – A selective β_3 -adrenoceptor agonist, potentially useful for the treatment of type 2 diabetes, obesity, gastrointestinal disorders and depression, as well as for reducing gut motility and neurogenic inflammation of the airways. Other exemplified amide derivatives are:



Compound	R1	R2	Isomer	Formula
309223	6-CN-2-Pyr	2-Pyr-CH2	S	C ₂₃ H ₂₃ N ₅ O ₂
309224	3-pyridazinyl	2-NH2-4-thiazolyl-CH2	S	C ₁₉ H ₂₂ N ₆ O ₂ S
309225	3-Me-5-isoxazolyl	2-NH2-4-thiazolyl-CH2	R	C ₁₉ H ₂₃ N ₅ O ₃ S
309226	3-CN-Ph	2-Pyr-CH2	R	C ₂₄ H ₂₄ N ₄ O ₂
309227	3-CN-Ph	2-NH2-4-thiazolyl-CH2	R	C ₂₂ H ₂₃ N ₅ O ₂ S
309228	2-Me-3-Pyr	2-Pyr-CH2	R	C ₂₃ H ₂₆ N ₄ O ₂
309229	2-Me-3-Pyr	2-NH2-4-thiazolyl-CH2	R	C ₂₁ H ₂₆ N ₅ O ₂ S
309230	3-Pyr	4-NH2-PhCH2	R	C ₂₃ H ₂₆ N ₄ O ₂
309231	6-NH2-3-Pyr	2-NH2-4-thiazolyl-CH2	R	C ₂₀ H ₂₄ N ₆ O ₂ S
309232	6-NH2-3-Pyr	2-Pyr-CH2	R	C ₂₂ H ₂₅ N ₅ O ₂
309233	6-NH2-3-Pyr	2-Pyr-CH2O	R	C ₂₂ H ₂₅ N ₅ O ₃

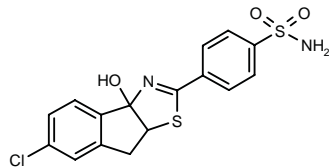
SOURCE – Merck & Co.

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1. Weber, A.E. et al. (Merck & Co., Inc.) *Amide derivs. as beta3 agonists*. US 6291491.

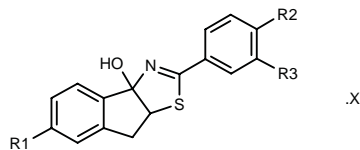
309444

4-(6-Chloro-3a-hydroxy-8,8a-dihydro-3a*H*-indeno[1,2-*d*]-thiazol-2-yl)benzenesulfonamide



C16 H13 Cl N2 O3 S2; Mol wt: 380.8747

ACTION – Anorectic agent, potentially useful for the treatment or prevention of obesity and type 2 diabetes. The compound decreased condensed milk consumption by 95% in fasted mice pretreated with 50 mg/kg p.o. Other exemplified compounds from this series of 8,8a-dihydro-3a*H*-indeno[1,2-*d*]thiazole derivatives include the following:



Compound	R1	R2	R3	X	Formula
309445	Cl	Cl	SO2NH2		C ₁₆ H ₁₂ Cl ₂ N ₂ O ₃ S ₂
309446	H	SO2NH2	H	HBr	C ₁₆ H ₁₄ N ₂ O ₃ S ₂ ·HBr

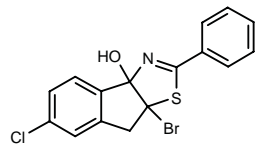
SOURCE – Aventis Pharma.

REFERENCES

1. Jaehne, G. et al. (Aventis Pharma Deutschland GmbH) *8,8a-Dihydro-indeno[1,2-d]-thiazole derivs. with a sulphonamido or sulphono substituent in the 2 position, a method for production thereof and use thereof as a medicament.* WO 0162747.

309447

8a-Bromo-6-chloro-2-phenyl-8,8a-dihydro-3a*H*-indeno[1,2-*d*]thiazol-3a-ol



C16 H11 Br Cl N O S; Mol wt: 380.6919

ACTION – Anorectic agent, potentially useful for the treatment or prevention of obesity and type 2 diabetes. The compound decreased condensed milk consumption by 82% in fasted mice pretreated with 50 mg/kg p.o. A representative compound from a series of 8,8a-dihydro-3a*H*-indeno[1,2-*d*]thiazole derivatives.

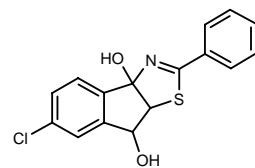
SOURCE – Aventis Pharma.

REFERENCES

1. Jaehne, G. et al. (Aventis Pharma Deutschland GmbH) *8,8a-Dihydro-indeno[1,2-d]-thiazole derivs., substd. in position 8a, a method for their production and their use as medicaments e.g. anorectic agents.* WO 0162746.

309448

6-Chloro-2-phenyl-8,8a-dihydro-3a*H*-indeno[1,2-*d*]-thiazole-3a,8-diol



C16 H12 Cl N O2 S; Mol wt: 317.7948

ACTION – Anorectic agent, potentially useful for the treatment or prevention of obesity and type 2 diabetes. The compound decreased condensed milk consumption by 31% in fasted mice pretreated with 30 mg/kg p.o. A representative compound from a series of 8,8a-dihydro-3a*H*-indeno[1,2-*d*]thiazole derivatives.

SOURCE – Aventis Pharma.

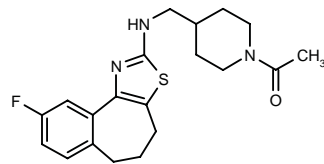
REFERENCES

1. Jaehne, G. et al. (Aventis Pharma Deutschland GmbH) *Substd. 8,8a-dihydro-3aH-indeno[1,2-d]thiazoles, a method for their production and their use as medicaments.* DE 10008274, WO 0162745.

309723

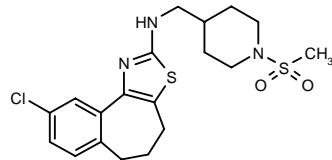
N-(1-Acetylpiperidin-4-ylmethyl)-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*]thiazol-2-amine

1-[4-(9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*]thiazol-2-ylaminomethyl)piperidin-1-yl]ethanone



C20 H24 F N3 O S; Mol wt: 373.4936

ACTION – Neuropeptide (NPY) Y₅ receptor antagonist, potentially useful for the treatment of eating disorders such as obesity, bulimia nervosa, diabetes and dyslipidemia, as well as other Y₅-mediated conditions including loss of memory, epilepsy, migraine, sleep disorders, pain, sexual disorders, depression, cerebral hemorrhage, hypertension and diarrhea. Another exemplified condensed thiazolamine is:



309724: C19 H24 Cl N3 O2 S2

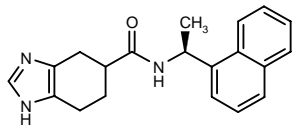
SOURCE – Novartis.

REFERENCES

1. Schmidlin, T. et al. (Novartis AG:Novartis-Erfindungen VmbH) *Condensed thiazolamines and their use as neuropeptide Y5 antagonists.* WO 0164675.

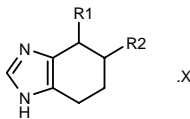
310043

N-[1(S)-(1-Naphthyl)ethyl]-4,5,6,7-tetrahydro-1H-benzimidazole-5-carboxamide



C20 H21 N3 O; Mol wt: 319.4059

ACTION – Histamine H₃ receptor modulator with potential in the treatment of obesity, eating disorders such as bulimia and anorexia, type 2 diabetes, impaired glucose tolerance, allergic rhinitis, ulcer, as well as disorders related to the 5-HT₃ receptor, vanilloid receptor and α₂-adrenoceptor including emesis, pain, neurogenic inflammation and sleep disorders. Other exemplified fused imidazole-containing compounds are:



Compound	R1	R2	X	Formula
310044	H	2,3-dihydro-7-benzofuryl-CH2NHCO		C ₁₇ H ₁₉ N ₃ O ₂
310049	H	bicyclo[2.2.1]hept-2-yl-NHCO		C ₁₅ H ₂₁ N ₃ O
310053	H	CONH(CH2)3Ph		C ₁₇ H ₂₁ N ₃ O
310054	H	2-(PhO)-PhCONH	HCl	C ₂₀ H ₁₉ N ₃ O ₂ .HCl
310055	H	cyclohexyl-NHCSNH		C ₁₄ H ₂₂ N ₄ S
310056	H	CONHPr		C ₁₁ H ₁₇ N ₃ O
310057	H	CONH(CH2)4OPh	HCl	C ₁₈ H ₂₃ N ₃ O ₂ .HCl
310058	H	4-Cl-Ph(CH2)3N(Me)CO	HCl	C ₁₈ H ₂₂ ClN ₃ O.HCl
310060	CON(Me)-CH2Ph	H		C ₁₆ H ₁₉ N ₃ O

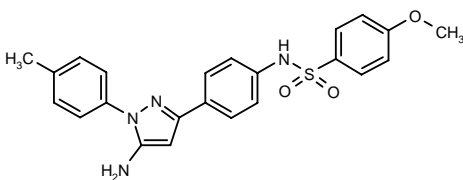
SOURCES – Boehringer Ingelheim; Novo Nordisk.

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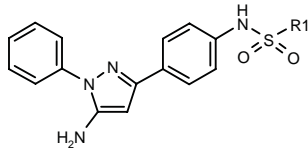
309449

N-[4-[5-Amino-1-(4-methylphenyl)-1H-pyrazol-3-yl]phenyl]-4-methoxybenzenesulfonamide

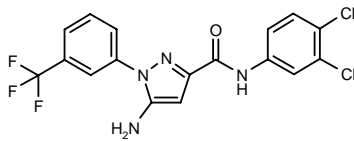


C23 H22 N4 O3 S; Mol wt: 434.5178

ACTION – Neuropeptide Y (NPY) Y₅ receptor ligand (IC₅₀ = 12 nM) with potential in the treatment of eating disorders (e.g., obesity, bulimia nervosa and anorexia nervosa), diabetes, dyslipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbances, pain, depression, anxiety, sexual/reproductive disorders, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea. Other exemplified 5-aminopyrazole compounds are:



Compound	R1	Formula
309450	Ph	C ₂₂ H ₂₀ N ₄ O ₂ S
309451	4-F-Ph	C ₂₂ H ₁₉ FN ₄ O ₂ S
309452	3-CF3-Ph	C ₂₃ H ₁₉ F ₃ N ₄ O ₂ S
309453	4-(CF3O)-Ph	C ₂₃ H ₁₉ F ₃ N ₄ O ₃ S
309454	2-Naph	C ₂₆ H ₂₂ N ₄ O ₂ S
309455	4-CF3-Ph	C ₂₃ H ₁₉ F ₃ N ₄ O ₂ S



309456: C17 H11 Cl2 F3 N4 O

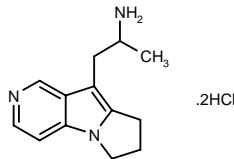
SOURCE – Ortho-McNeil.

REFERENCES

1. Kordik, C.P. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Amino pyrazole derivs. useful in the treatment of obesity and other disorders*. WO 0162737.

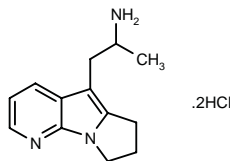
309610

1-(7,8-Dihydro-6H-pyrido[3,4-b]pyrrolizin-9-yl)propan-2-amine dihydrochloride



C13 H17 N3 . 2HCl; Mol wt: 288.2201

ACTION – Selective 5-HT_{2C} receptor agonist, potentially useful for the treatment of obesity, meningitis, thrombosis and gastrointestinal motility dysfunction. Another exemplified azaindolyl derivative is:



309611: C13 H17 N3 . 2HCl

SOURCES – Roche; Vernalis.

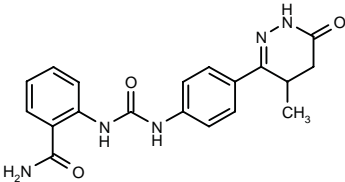
REFERENCES

1. Bentley, J.M. et al. (Vernalis Research Ltd.;F. Hoffmann-La Roche AG) *New aza-indolyl derivs. for the treatment of obesity*. EP 1132389, WO 0166548.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

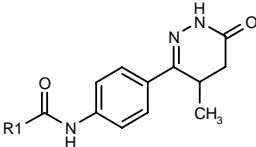
309775

2-[3-[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-phenyl]ureido]benzamide



C19 H19 N5 O3; Mol wt: 365.3911

ACTION – Erythropoiesis-stimulating agent, potentially useful for the prevention and treatment of anemia. Other exemplified 4-methylpyridazinones are:



Compound	R1	Formula
309776	3-Cl-Ph	C ₁₈ H ₁₆ ClN ₃ O ₂
309777	cycloheptyl	C ₁₉ H ₂₅ N ₃ O ₂
309778	4-MeO-PhNH	C ₁₉ H ₂₀ N ₄ O ₃
309779	4-(4-Me-6-oxo-1,4,5,6-tetrahydro-3-pyridazinyl)-PhNH	C ₂₃ H ₂₄ N ₆ O ₃

SOURCE – Bayer.

REFERENCES

1. Bräunlich, G. et al. (Bayer AG) *Substd. 5-methyldihydropyridazinones and their use in the prophylaxis and/or treatment of anemias*. DE 10010425, WO 0164652.

THERAPY OF INBORN ERRORS
OF METABOLISM

AGALSIDASE BETA

Prop INN

284540

α-Galactosidase (human clone λAG¹⁸ isoenzyme A subunit protein moiety reduced), glycoform β

ACTION – Recombinant form of α-galactosidase A that clears globotriaosylceramide (GL-3) from the vascular endothelium of the kidneys.

INDICATION – Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry’s disease.

PRESENTATION – Vials containing 35 mg agalsidase beta as powder for concentrate for solution for infusion, for reconstitution with 7.2 ml water for injection (5 mg/ml).

PROPRIETARY NAME – Fabrazyme (DE, GB, SE).

SOURCE – Genzyme General.

REFERENCES

1. Eng, C.M. et al. *Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry’s disease*. New Engl J Med 2001, 345(1): 9.

2. Eng, C.M. et al. *Enzyme replacement therapy in Fabry disease: Results of a placebo-controlled phase 3 trial*. Am J Hum Genet 2000, 67(4, Suppl. 2): Abst 134.

3. Eng, C.M. et al. *A phase 1/2 clinical trial of enzyme replacement in Fabry disease: Pharmacokinetic, substance clearance, and safety studies*. Am J Hum Genet 2001, 68(3): 711.

4. Ioannou, Y.A. et al. *Fabry disease: Preclinical studies demonstrate the effectiveness of α-galactosidase A replacement in enzyme-deficient mice*. Am J Hum Genet 2001, 68(1): 14.

5. *CPMP issues positive opinion for Fabrazyme*. DailyDrugNews.com (Daily Essentials) 2001, March 30.

6. *Fabrazyme advisory committee review not necessary*. DailyDrugNews.com (Daily Essentials) 2000, Nov 6.

7. *Fabrazyme available to Fabry’s disease patients in several E.U. countries*. DailyDrugNews.com (Daily Essentials) 2001, Oct 30.

8. *Fabrazyme meets primary endpoint in pivotal trial of Fabry’s disease*. DailyDrugNews.com (Daily Essentials) 2000, Oct 16.

9. *Genzyme General announces record fourth-quarter and 1999 revenues*. Genzyme General Press Release 2000, Jan 11.

10. *Genzyme General begins treating Fabry disease patients; global disease registry launched*. DailyDrugNews.com (Daily Essentials) 2001, Jan 22.

11. *Genzyme General continues to make good progress in advancing development programs*. DailyDrugNews.com (Daily Essentials) 2001, July 23.

12. *Genzyme General files BLA for approval to market Fabrazyme*. DailyDrugNews.com (Daily Essentials) 2000, June 27.

13. *Genzyme General files MAA for approval of Fabrazyme in Europe*. DailyDrugNews.com (Daily Essentials) 2000, July 20.

14. *Genzyme General highlights Q3 developments*. DailyDrugNews.com (Daily Essentials) 2001, Oct 26.

15. *Genzyme General reports Q1 2001 update*. DailyDrugNews.com (Daily Essentials) 2001, May 21.

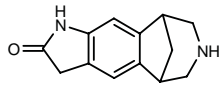
16. *Genzyme General updates progress on development programs*. DailyDrugNews.com (Daily Essentials) 1999, Oct 19.

17. *Genzyme General's BLA for Fabry's disease accepted by FDA.* DailyDrugNews.com (Daily Essentials) 2000, Sept 22.
18. *Genzyme General: Q1 1999 highlights.* DailyDrugNews.com (Daily Essentials) 1999, April 30.
19. *Genzyme receives FDA complete response letter for Fabrazyme.* DailyDrugNews.com (Daily Essentials) 2001, Aug 25.
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22. *Pivotal trial of Fabrazyme meets primary endpoint.* DailyDrugNews.com (Daily Essentials) 2000, May 5.
23. *Proposed international nonproprietary names (Prop. INN): List 84.* WHO Drug Inf 2000, 14(4): 248.
24. *Update on status of Fabrazyme reported by Genzyme General.* DailyDrugNews.com (Daily Essentials) 2001, Jan 3.

TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

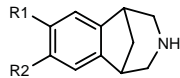
309458

1,2,3,5,6,7,8,9-Octahydro-5,9-methanoazepino[4,5-*f*]-indol-2-one



C13 H14 N2 O; Mol wt: 214.2666

ACTION – Agent with affinity for neuronal nicotinic acetylcholine receptors, potentially useful for reducing nicotine addiction or aiding in the cessation or lessening of cigarette smoking. Other uses include the treatment of inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum, Crohn’s disease, irritable bowel syndrome, spastic dystonia, pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorders, depression, etc. Other specifically claimed aryl fused azapolycyclic compounds are:



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309460	-SO ₂ N=C[N(Me)2]-	C ₁₄ H ₁₇ N ₃ O ₂ S
309461	-N(Me)COCON(Me)-	C ₁₅ H ₁₇ N ₃ O ₂
309462	-OCON(Me)-	C ₁₃ H ₁₄ N ₂ O ₂

SOURCE – Pfizer.

REFERENCES

1. Brooks, P.R.P. and Coe, J.W. (Pfizer Products Inc.) *Aryl fused azapolycyclic cpds.* WO 0162736.

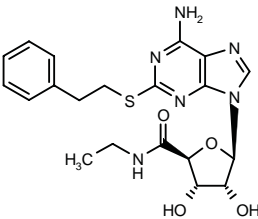
DIAGNOSTIC AGENTS

309443

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N-Ethyl-1-[2-(2-phenylethylsulfanyl)adenin-9-yl]-β-D-ribofuranuronamide



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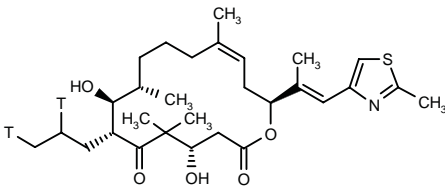
SOURCE – CV Therapeutics.

REFERENCES

1. Cristalli, G. (CV Therapeutics, Inc.) *2-Thioether A_{2A} receptor agonists.* WO 0162768.

310154

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C29 H43 N O5 S T2; Mol wt: 523.7587

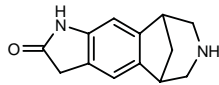
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TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

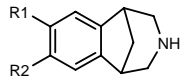
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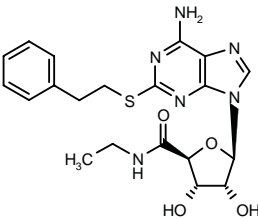
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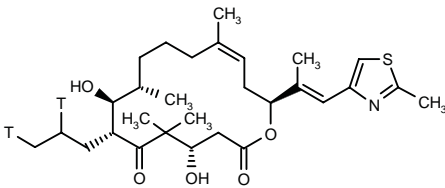
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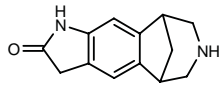
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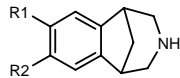
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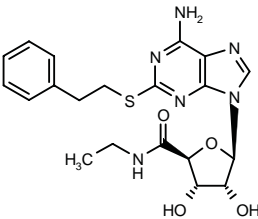
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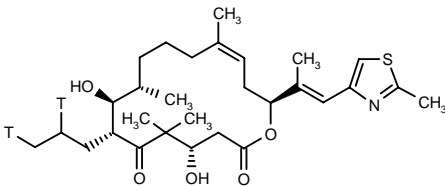
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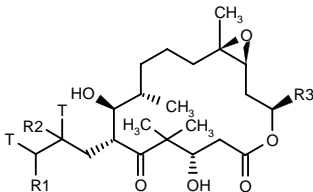
310154

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Compound	R1	R2	R3	Formula
310155	H	H	(E)-2-Me-4-thiazolyl-CH=C(Me)	C ₂₉ H ₄₃ NO ₆ ST ₂
310156	H	H	2-Me-5-benzothiazolyl	C ₃₀ H ₄₁ NO ₆ ST ₂
310157	bond		2-Me-5-benzothiazolyl	C ₃₀ H ₃₉ NO ₆ ST ₂

SOURCE – Schering AG.

REFERENCES

1. Klar, U. et al. (Schering AG) *Radioactively labeled epothilone derivs., method for the production thereof, and their biochemical and pharmaceutical use.* WO 0166154.

PB-127

296093

Ultrasound imaging agent composed of nitrogen gas encapsulated in highly echogenic bispheres (bilayer microspheres) comprised of an outer layer of human albumin and an inner layer of a biodegradable polymer

ACTION – Agent for power Doppler imaging of coronary arteries consisting of bilayered, nitrogen-filling microspheres, able to produce complete opacification of the left ventricular (LV) cavity and all myocardial segments without significant posterior attenuation. In phase I clinical trials in healthy volunteers, single i.v. bolus injection was well tolerated and produced dense LV cavity filling in both gray scale and power Doppler in all subjects, as well as intense and homogeneous myocardial opacification. Moreover, in dogs with three left anterior descending (LAD) coronary stenoses, i.v. infusion of compound during triggered power Doppler imaging and myocardial contrast echocardiography (MCE) produced excellent images of coronary stenoses when performed with adenosine stress.

SOURCE – Point Biomedical.

REFERENCES

1. Ottoboni, T.B. et al. (Point Biomedical Corporation) *Microparticles useful as ultrasonic contrast agents.* US 6193951.

2. Cotter, B. et al. *PB 127, a new bilayer ultrasound contrast agent produces complete opacification of the LV cavity and all myocardial segments with minimal attenuation: Phase I experience following bolus intravenous injection.* Circulation 2000, 102(18, Suppl.): Abst 2725.

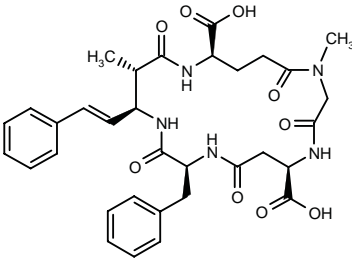
3. Demaria, A. et al. *PB127 phase 2 trial results: Concordance of perfusion echocardiography with stress SPECT.* Circulation 2001, 104(17, Suppl. 2): Abst 2353.

4. Villanueva, F.S. et al. *Detection of coronary artery stenosis with power Doppler imaging.* Circulation 2001, 103(21): 2624.

PHARMACOLOGICAL TOOLS

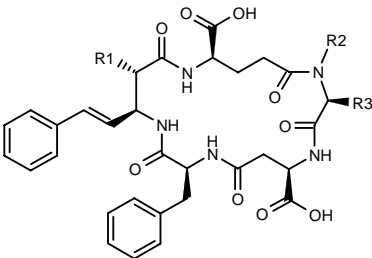
309359

9(S)-Benzyl-1,13(S)-dimethyl-3,7,10,14,19-pentaoxo-12(S)-(2-phenylvinyl)-1,4,8,11,15-pentaazacyclononadecane-5(R),16(R)-dicarboxylic acid



C33 H39 N5 O9; Mol wt: 649.6971

ACTION – Serine–threonine protein phosphatase (PP) inhibitor selective for the catalytic subunit of PP1 (K_i = 206 μM). Potentially useful as a pharmacological tool to elucidate the pathophysiological role of the enzyme. Other related compounds are:

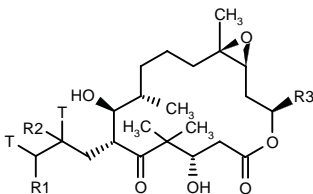


Compound	R1	R2	R3	Formula
309358	H	Me	H	C ₃₂ H ₃₇ N ₅ O ₉
309360	Me	-(CH2)3-		C ₃₅ H ₄₁ N ₅ O ₉

SOURCE – University of Birmingham, Birmingham (GB).

REFERENCES

1. O'Donnell, M.E. et al. *Serine-threonine protein phosphatase inhibitors derived from nodularin: Role of the 2-methyl and 3-diene groups in the Adda residue and the effect of macrocyclic conformational restraint.* J Chem Soc - Perkins Trans I 2001, (14): 1696.



Compound	R1	R2	R3	Formula
310155	H	H	(E)-2-Me-4-thiazolyl-CH=C(Me)	C ₂₉ H ₄₃ NO ₆ ST ₂
310156	H	H	2-Me-5-benzothiazolyl	C ₃₀ H ₄₁ NO ₆ ST ₂
310157	bond		2-Me-5-benzothiazolyl	C ₃₀ H ₃₉ NO ₆ ST ₂

SOURCE – Schering AG.

REFERENCES

1. Klar, U. et al. (Schering AG) *Radioactively labeled epothilone derivs., method for the production thereof, and their biochemical and pharmaceutical use.* WO 0166154.

PB-127

296093

Ultrasound imaging agent composed of nitrogen gas encapsulated in highly echogenic bispheres (bilayer microspheres) comprised of an outer layer of human albumin and an inner layer of a biodegradable polymer

ACTION – Agent for power Doppler imaging of coronary arteries consisting of bilayered, nitrogen-filling microspheres, able to produce complete opacification of the left ventricular (LV) cavity and all myocardial segments without significant posterior attenuation. In phase I clinical trials in healthy volunteers, single i.v. bolus injection was well tolerated and produced dense LV cavity filling in both gray scale and power Doppler in all subjects, as well as intense and homogeneous myocardial opacification. Moreover, in dogs with three left anterior descending (LAD) coronary stenoses, i.v. infusion of compound during triggered power Doppler imaging and myocardial contrast echocardiography (MCE) produced excellent images of coronary stenoses when performed with adenosine stress.

SOURCE – Point Biomedical.

REFERENCES

1. Ottoboni, T.B. et al. (Point Biomedical Corporation) *Microparticles useful as ultrasonic contrast agents.* US 6193951.

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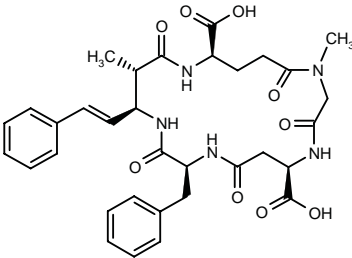
3. Demaria, A. et al. *PB127 phase 2 trial results: Concordance of perfusion echocardiography with stress SPECT.* Circulation 2001, 104(17, Suppl. 2): Abst 2353.

4. Villanueva, F.S. et al. *Detection of coronary artery stenosis with power Doppler imaging.* Circulation 2001, 103(21): 2624.

PHARMACOLOGICAL TOOLS

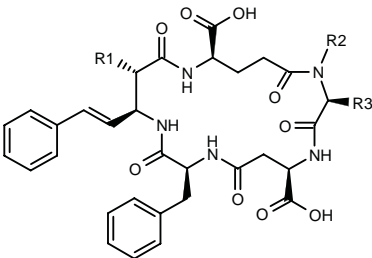
309359

9(S)-Benzyl-1,13(S)-dimethyl-3,7,10,14,19-pentaoxo-12(S)-(2-phenylvinyl)-1,4,8,11,15-pentaazacyclononadecane-5(R),16(R)-dicarboxylic acid



C33 H39 N5 O9; Mol wt: 649.6971

ACTION – Serine–threonine protein phosphatase (PP) inhibitor selective for the catalytic subunit of PP1 (K_i = 206 μM). Potentially useful as a pharmacological tool to elucidate the pathophysiological role of the enzyme. Other related compounds are:



Compound	R1	R2	R3	Formula
309358	H	Me	H	C ₃₂ H ₃₇ N ₅ O ₉
309360	Me	-(CH ₂) ₃ -		C ₃₅ H ₄₁ N ₅ O ₉

SOURCE – University of Birmingham, Birmingham (GB).

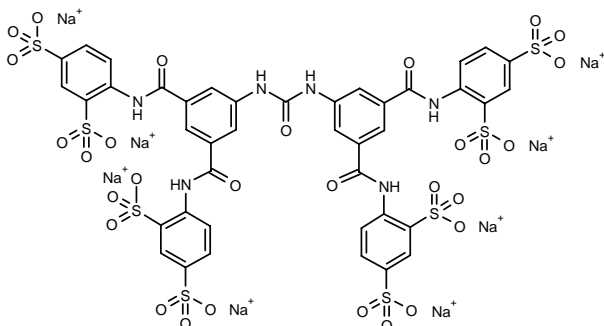
REFERENCES

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NF-449

263902

4,4',4'',4'''-(1,3-Ureylene)bis(5,1,3-benzenetriyl)bis-(carbonylimino)tetrakis(benzene-1,3-disulfonic acid) octa-sodium salt



C41 H24 N6 Na8 O29 S8; Mol wt: 1505.1020

ACTION – Purine P2X₁ receptor antagonist (pIC₅₀ = 7.15 and 9.54, respectively, for functional antagonism of native rat vas deferens receptors and recombinant receptors) with less activity at P2X₃ and P2Y₁ receptors expressed in guinea pig ileum (pIC₅₀ = 5.04 and 4.85, respectively) and P2Y₂ receptors in HEK 293 cells (pIC₅₀ = 3.86). Moreover, compound at 100 μM did not interact with α₁-adrenoceptors, histamine H₁ or muscarinic M₃ receptors. Potentially useful as a pharmacological tool for the characterization of P2X₁ receptors.

SOURCES – Universität Bonn, Bonn (DE); Johann Wolfgang Goethe Universität, Frankfurt (DE); Universität Wien, Vienna (AT).

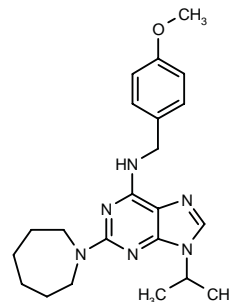
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4. Hohenegger, M. et al. *Gsα-selective G protein antagonists*. Proc Natl Acad Sci USA 1998, 95(1): 346.

NG-38

306501

9-Isopropyl-N-(4-methoxybenzyl)-2-(perhydroazepin-1-yl)-9H-purin-6-amine



C22 H30 N6 O; Mol wt: 394.5200

ACTION – Potent and selective inhibitor of estrogen sulfotransferase (EST; IC₅₀ = 0.5 μM) with moderate activity against the cyclin-dependent kinase CDK1 (IC₅₀ = 4 μM). Potentially useful as a pharmacological tool to elucidate the role of EST in steroid homeostasis and tumor cell proliferation.

SOURCE – Novartis.

REFERENCES

1. Chang, Y.-T. et al. *Synthesis and application of functionally diverse 2,6,9-trisubstituted purine libraries as CDK inhibitors*. Chem Biol 1999, 6(6): 361.
2. Verdugo, D.E. et al. *Discovery of estrogen sulfotransferase inhibitors from a purine library screen*. J Med Chem 2001, 44(17): 2683.